University of Alberta

Investigating Bipolar Depression in an outpatient psychiatric population: Prevalence Rates and Differentiation from Unipolar Depression.

by

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ABSTRACT

The diagnosis of bipolar depression is frequently missed in clinical practice. In this thesis, we measured the prevalence of bipolar depression among 315 consecutive patients referred to a mood disorder outpatient clinic. In this population, we diagnosed 62 patients with bipolar depression, and an additional 187 patients with unipolar major depressive disorder (UMDD). We then compared the bipolar depressed group with the UMDD group and found differences in regards to comorbidities and other measurements. We were also interested in the frequency of bipolar spectrum disorder in this population, and diagnosed this in a further 39 patients. There were thus a total of 101 patients (32%) of the original patient population who had some form of bipolar disorder, most of whom had not been diagnosed accurately. We did not find any significant differences between the bipolar depressed group and the bipolar spectrum disorder group.

Dedication:

To Philipus and Sophia Wessels,
my parents

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Table of Contents:

1 INTRODUCTION AND THESIS OUTLINE 1

2 PREVALENCE OF BIPOLAR DEPRESSION IN A CONSECUTIVE SAMPLE OF 315 PATIENTS SEEN AT THE MOOD DISORDER CLINIC 5

2.1 DEFINING BIPOLAR DISORDERS 5
2.1.1 DEFINING MOOD DISORDERS ACCORDING TO DSM-IV CRITERIA 5
2.1.2 DIFFERENT APPROACHES TO DEFINING BIPOLAR DISORDERS 6
2.1.2.1 Subsyndromal approaches 6
2.1.2.2 Bipolar Spectrum approach 7
2.1.2.3 Integration of mood and personality 11
2.1.2.4 Definitions according to symptomatology 12
2.2 COURSE AND PROGRESSION OF BIPOLAR DISORDER 13
2.3 INCIDENCE AND PREVALENCE OF BIPOLAR DISORDER 18
2.4 PREVELANCE WHEN MEASURING BIPOLAR SPECTRUM DISORDERS 20
2.5 MISDIAGNOSIS AND OVERLAP BETWEEN MAJOR DEPRESSIVE DISORDER AND SUB-THRESHOLD BIPOLAR DISORDER 22

3 COMORBIDITY OF BIPOLAR DISORDER 24

3.1 ANXIETY DISORDERS 26
3.2 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD). 28
3.3 EATING DISORDERS. 29
3.4 ALCOHOL AND SUBSTANCE USE DISORDERS. 30
3.5 COMORBID PERSONALITY DISORDERS. 31
3.6 MEDICAL COMORBIDITIES: SYMPTOMS CONSISTENT WITH THE METABOLIC SYNDROME 33
3.7 SUICIDE 36
3.8 DEFINITION OF ATYPICAL DEPRESSION AND RELEVANCE TO BIPOLAR DEPRESSION 38

4 STUDY METHODOLOGY FOR ASSESSMENT OF OUTPATIENTS 41

4.1 DEFINITION OF SAMPLE 41
4.2 METHODOLOGY FOR SCREENING PATIENTS 42
4.2.1 MAJOR DSM-IV AXIS 1 DIAGNOSES 43
4.2.2 COMORBIDITIES 45
4.2.2.1 MAJOR COMORBID DSM-IV AXIS 1 or II DIAGNOSES 45
4.2.2.2 B. COMORBID MEDICAL PROBLEMS 46
4.2.2.3 COMORBID ALCOHOL AND SUBSTANCE ABUSE DISORDERS 47
4.2.3 OTHER MEASUREMENTS 48
4.2.3.1 AGE 48
4.2.3.2 GENDER 48
4.2.3.3 EMPLOYMENT STATUS 48
4.2.3.4 MARITAL STATUS 49
4.2.3.5 REASON FOR REFERRAL 49
4.2.3.6 PRIOR PSYCHIATRIC HISTORY 50
4.2.3.7 FAMILY HISTORY OF PSYCHIATRIC PROBLEMS 51

5 DESCRIPTIVE RESULTS FROM ALL PATIENTS INVOLVED IN OUTPATIENT STUDY 52

5.1 MAJOR AXIS 1 DSM-IV DIAGNOSIS 52
5.2 COMORBIDITIES 52
5.2.1 COMORBID PSYCHIATRIC DIAGNOSIS 52
5.2.2 COMORBID MEDICAL DIAGNOSIS 53
5.2.3 SUBSTANCE COMORBIDITIES 53

5.3 OTHER MEASUREMENTS 54
5.3.1 AGE *54*
5.3.2 GENDER *54*
5.3.3 EMPLOYMENT STATUS *54*
5.3.4 MARITAL STATUS *54*
5.3.5 REASON FOR REFERRAL *55*
5.3.6 PRIOR PSYCHIATRIC HISTORY *55*
5.3.7 FAMILY HISTORY OF PSYCHIATRIC PROBLEMS *55*

6 DISCUSSION OF THESE RESULTS **56**

7 COMPARISON OF 62 BIPOLAR DEPRESSED PATIENTS WITH 187 UMDD PATIENTS **58**

7.1 METHODOLOGY COMPARING 62 BIPOLAR DEPRESSED PATIENTS WITH 187 UMDD PATIENTS 58
7.2 RESULTS 59
7.2.1 COMORBIDITIES *59*

8 DISCUSSION OF RESULTS. **74**

8.1 COMORBIDITIES 74
8.1.1 ANXIETY DISORDER *74*
8.1.2 SUBSTANCE USE DISORDER *75*
8.1.3 PERSONALITY DISORDER AS A COMORBID DIAGNOSIS *77*
8.1.4 ATTENTION-DEFECIT/ HYPERACTIVITY DISORDER *78*
8.1.5 MEDICAL COMORBIDITIES *79*
8.2 OTHER MEASURES. 80
8.2.1 AGE. *80*
8.2.2 GENDER *81*
8.2.3 EMPLOYMENT STATUS *81*
8.2.4 MARITAL STATUS: SINGLE OR NEVER MARRIED *83*
8.2.5 REASON FOR REFERRAL *83*
8.2.6 PRIOR PSYCHIATRIC HISTORY *85*
8.2.7 FAMILY HISTORY *85*

9 PRESENCE OF BIPOLAR SPECTRUM DISORDER IN 315 CONSECUTIVE OUTPATIENTS. **87**

9.1 METHODOLOGY OF SCREENINGS 88
9.2 RESULTS SHOWING NUMBERS IN EACH MAJOR DIAGNOSTIC GROUPING ... 90
9.3 RESULTS COMPARING 62 BIPOLAR DEORESSED PATIENTS WITH 39 BIPOLAR SPECTRUM PATIENTS 92
9.3.1 COMPARISON IN REGARDS TO COMORBIDITIES AMONG 62 BIPOLAR DEPRESSED PATIENTS AND 39 BIPOLAR SPECTRUM PATIENTS *92*
9.3.2 OTHER MEASUREMENTS *97*

10 DISCUSSION OF COMPARISON BETWEEN BIPOLAR DEPRESSED GROUP AND BIPOLAR SPECTRUM **105**

10.1 SUMMARY OF STATISTICAL FINDINGS 105
10.1.1 COMORBIDITIES *105*
10.1.1.1 Comorbid major diagnoses. 105
10.1.2 OTHER MEASUREMENTS *106*
10.1.2.1 Age. 106
10.1.2.2 Gender 107
10.1.2.3 Employment status. 108
10.1.2.4 Marital status: single or never married. 108
10.1.2.5 Reason for referral and prior psychiatric history. 109
10.1.2.6 Family history of psychiatric illness. 109
10.2 FREQUENCY 109

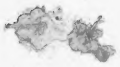
11 MEASUREMENT OF SEVERITY OF DEPRESSION 113

11.1 PATIENT POPULATION USED TO COMPARE HAMD-17 AND MADRS 115
11.2 DISCUSSION OF FINDINGS 119

12 SUMMARY OF FINDINGS AND CONCLUSIONS FROM THESIS 120

12.1 WEAKNESSES OF STUDY DESIGN 120
12.2 SUMMARY OF FINDINGS. 121
12.3 CONCLUSION. 124
12.4 FUTURE DIRECTIONS 126

13 REFERENCES AND BIBLIOGRAPHY 130



List of Tables:

Table 1 Comparing 62 patients with bipolar depression and 187 with UMDD in regards to comorbidities and other measurements.....128

Table 2 Comparing 62 patients with bipolar depression and 39 with bipolar spectrum disorder in regards to comorbidities and other measurements.....129

List of Figures:

7.2.1.1 Pearson's exact test comparing bipolar depression and UMDD in regards to comorbid anxiety disorders.....59

7.2.1.2 Pearson's exact test comparing bipolar depression and UMDD in regards to substance use disorder comorbidity.....60

7.2.1.3 Pearson's exact test comparing bipolar depression and UMDD in regards to a history of any substance use disorder.....61

7.2.1.4 Pearson's exact test comparing bipolar depression and UMDD in regards to comorbid personality disorder.....62

7.2.1.5 Pearson's exact test comparing bipolar depression and UMDD in regards to risk factors for metabolic syndrome.....63

7.2.2.1 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age groups 18-35.....64

7.2.2.2 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age group 36-49.....65

7.2.2.3 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age group older than 50.....66

7.2.2.4 Pearson's exact test comparing bipolar depression and UMDD in regards to gender.....67

7.2.2.5 Pearson's exact test comparing bipolar depression and UMDD in regards to unemployment.....68

7.2.2.6 Pearson's exact test comparing bipolar depression and UMDD in regards to single patients.....69

7.2.2.7 Pearson's exact test comparing bipolar depression and UMDD in regards to depressed mood as reason for referral.....70

7.2.2.8 Pearson's exact test comparing bipolar depression and UMDD in regards to "mood swings of unknown origin" as reason for referral.....71

7.2.2.9 Pearson's exact test comparing bipolar depression and UMDD in regards to a prior history of UMDD.....72

7.2.2.10 Pearson's exact test comparing bipolar depression and UMDD in regards to a family history of mood disorder.....73

9.3.1.1 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to anxiety disorder as comorbidity.....92

9.3.1.2 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to any substance use comorbidity.....93

9.3.1.3 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to a prior history of any substance use disorder.....94

9.3.1.4 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to personality disorder as comorbidity.....95

9.3.1.5 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to risk factors for metabolic syndrome.....96

9.3.2.1 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to age group: 18-49.....97

9.3.2.2 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to gender.....98

9.3.2.3 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to being unemployed.....99

9.3.2.4 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to being single or never married.....100

9.3.2.5 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to depressed moods as reason for referral.....101

9.3.2.6 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to "mood swings of unknown origin" as reason for referral.....102

9.3.2.7 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to a prior psychiatric history of UMDD.....103

9.3.2.8 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to a family history of mood disorders.....104

11.1.1 Chi-square test comparing HAM-D17 and MADRS among patients with UMDD.....117

11.1.2 Chi-square test comparing HAM-D17 and MADRS among patients with bipolar depression.....118

1 INTRODUCTION AND THESIS OUTLINE

The ancient Greeks like Aristotle and Hippocrates have described mania and melancholia as separate disease states. However, the first person to describe mania and melancholia as two different phenomenological states of the same illness was perhaps the first century AD physician, Aretaeus of Cappadocia (Angst et al., 2001).

Bipolar disorder is differentiated from unipolar major depressive disorder (UMDD) by the presence of periods of depressive mood, which are similar to those seen in UMDD, but in which the patient also experiences periods of mood elevation, either manic or hypomanic. Nonetheless, in comparison to UMDD, which is well defined in terms of nosology and has well-established treatment options, the same cannot be said for major depressive disorder in the context of bipolar disorder ("bipolar depression"). This is despite the fact that most patients with bipolar disorder spend the large majority of their time when ill in a depressed state (Judd et al., 2002). Currently, there remains a relatively poor understanding of the frequency of bipolar depression. As a psychiatrist in clinical practice, the author was particularly interested whether it was under-diagnosed in clinical practice, and how it might differ from UMDD.

Of note is that bipolar disorder is frequently associated with symptoms of other comorbid conditions, both psychiatric and medical, such as anxiety disorders

(McElroy et al., 2001). This co-occurrence is so frequent that it has been argued that having a comorbid condition in bipolar disorder is the rule rather than the exception (Baldassano, 2006). Comorbid psychiatric diagnoses, including substance use disorders, make the diagnosis of bipolar disorder more problematic. Additionally, comorbid diagnoses, whether psychiatric or medical, impact patients in terms of illness severity, morbidity and mortality. They also have treatment implications, since it is more difficult to manage these patients pharmacologically (McElroy et al., 2004; Henry et al., 2003). Accurate diagnosis can also be difficult since diagnoses according to the Diagnostic and Statistic Manual, 4th edition of the American Psychiatric Association (DSM-IV) specifically precludes a diagnosis of a mood disorder when symptoms may be present due to substance abuse, other medication use, the presence of a medical condition, and during bereavement. Understanding how frequently such comorbid psychiatric and physical conditions occur in bipolar depressed patients has been relatively poorly researched to date, particularly in psychiatric clinic populations. It has also been proposed that this is particularly misdiagnosed in patients who are otherwise seen simply as having UMDD (Ghaemi et al., 2001 and 2002; Akiskal et al., 2006, and Berk et al., 2006), a suggestion that hasn't been widely studied.

In addition, there is a concern about the relevance of the current operational criteria used to define that a significant mood-elevating event has occurred. Thus, current diagnostic criteria for bipolar disorder in DSM-IV require that for a diagnosis of mania the period of elevated mood must be at least 7 days (or lead to

a hospital admission), and that for a diagnosis of hypomania the period of elevated mood must be present for at least 4 days. Nonetheless, there is little empirical data that these lengths of time have any validity. Given difficulties with diagnosing bipolar disorder, and the fact that current criteria differentiate only due to length of time and severity of the periods of mood elevation, others have suggested the concept of a "bipolar spectrum disorder" in which subjects who experience periods of mood elevation that do not meet current diagnostic criteria are nonetheless considered as clinically significant (Akiskal et al., 1999). This approach is becoming more widely studied, and several authors have used broader criteria for hypomania in their studies (Angst, 2007; Rybakowski et al., 2007; Akiskal et al., 2006; Kiejna et al., 2005).

Given all of these issues, the studies presented in this thesis were designed to help elucidate some of these underlying issues. The first part of the study looks at the diagnostic breakdown among the total patient population of 315 consecutive patients referred to a specific mood-disorders clinic. Of these patients, it was determined that a total of 187 patients had a primary diagnosis of UMDD, and 62 patients had a primary diagnosis of bipolar depression according to DSM-IV criteria. The major part of this thesis is a comparison between these two groups. Further analysis showed that in addition to the 62 patients who met criteria for bipolar depression according to DSM-IV criteria, there were an additional 39 patients who met various criteria for bipolar spectrum disorder, and these two groups are then compared.

In addition, a small percentage of these patients also agreed to additional interviews (as approved by the Research Ethics Board of the University of Alberta) with a view to partaking in various psychiatric imaging studies (not part of this thesis). As part of these assessments they completed standardized psychiatric measurement scales for depressed and elevated mood, and this thesis examines differences in these scales between the UMDD and bipolar depression groups in this subset of the patient population.

In summary, this thesis was designed to measure the prevalence of bipolar disorder in this population, particularly in a population that had been diagnosed originally primarily with UMDD. It was also designed to examine differences between bipolar depression and unipolar major depressive disorder, examine the effects of different diagnostic criteria on the frequency of bipolar depression, and determine the frequency of many other possibly relevant factors in this population such as comorbidities and other measurements. Furthermore the prevalence of Bipolar Spectrum Disorder was established among the entire patient population. Those patients who fulfilled the criteria for Bipolar Spectrum Disorder, according to Ghaemi and colleagues' criteria (2002) were then compared with those who were diagnosed with Bipolar Depression in regards to comorbidities and other measurements.

2 PREVALENCE OF BIPOLAR DEPRESSION IN A CONSECUTIVE SAMPLE OF 315 PATIENTS SEEN AT THE MOOD DISORDER CLINIC

2.1 Defining Bipolar Disorders

2.1.1 DEFINING MOOD DISORDERS ACCORDING TO DSM-IV CRITERIA

According to DSM-IV, there are two major types of mood disorder, unipolar major depressive disorder (UMDD) in which patients only experience a depressed mood, and bipolar disorder, in which patients also experience periods of elevated mood in addition to periods of depressed mood. Bipolar disorder has two subtypes defined in DSM-IV, depending on the length and severity of the mood elevation. In both subtypes, bipolar disorder type I (bipolar I disorder) and bipolar disorder type II (bipolar II disorder) major depressive episodes also occur. In bipolar I disorder there must be at least one manic episode present, where symptoms must be present for at least a week, or any duration when hospitalization is required (DSM-IV, 1994). It is accompanied by major depressive episodes, as well as hypomanic and mixed episodes over time. Mixed episodes are defined by the simultaneous, and significant presence of both manic and depressive symptoms. In contrast a history of one or more major depressive episodes as well as a history of at least one hypomanic episode, in which symptoms of elevated mood last at least four days, characterize bipolar II disorder (DSM-IV, 1994). DSM-IV recognizes other disorders in which mood elevation can occur, for example cyclothymic disorder is another chronic mood syndrome with hypomanic and

depressive symptoms that do not meet the threshold criteria for a major depressive episode. There is also a bipolar disorder not otherwise specified category that includes disorders with bipolar symptoms that do not meet criteria for any bipolar disorder.

2.1.2 DIFFERENT APPROACHES TO DEFINING BIPOLAR DISORDERS

2.1.2.1 *Subsyndromal approaches*

While DSM-IV criteria are useful in both the clinical and research realms, several authors have argued that its categorical approach is too simplistic (Angst, 2007; Merikangas et al., 2007; Akiskal et al., 2006; and Ghaemi et al., 2001 and 2002). These authors have suggested that instead of discrete entities, bipolar disorders in fact occupy a spectrum of disorders with no clear demarcation between conditions. The more classic representation whereby bipolar I and bipolar II disorders consist of well-demarcated mood episodes, interspersed with symptom-free intervals, is increasingly being replaced by one which encompasses a bipolar spectrum disorder. This includes subsyndromal forms of both elevated and depressed mood. It has been suggested that bipolar spectrum disorders are disabling and as least as common as more "classical" bipolar I disorder (Akiskal et al., 2000; Ghaemi et al., 2002; Berk et al., 2005; Angst, 2007). Akiskal and colleagues (2005) have also argued that the current criteria required to fulfill a diagnosis of a hypomanic episode (needed to diagnose bipolar I or II disorders)

are too strict and exclude a lot of patients with conditions that impact them significantly. In research to support these suggestions they have applied modified criteria where they've used a duration of 2 or more days of hypomania, instead of the four-day cut-off period needed to make a diagnosis of hypomania according to DSM-IV. They have suggested that such a disorder often occurs in patients who had previously only been diagnosed as having UMDD. Thus, in their studies they found that such a modified form of bipolar II disorder occurred in 56.8% of consecutive outpatients who until that time only had a diagnosis of major depressive disorder (Akiskal et al., 2005). Further support for this hypothesis comes from Angst (2006) who suggested that 40% to 60% of patients in psychiatric practice with a diagnosis of major depressive disorder should have received a diagnosis of bipolar II disorder. According to Angst the duration for hypomania should be reduced to less than 4 days, as the majority of patients with bipolar II disorder have episodes of hypomania that last 1 to 3 days (Angst J, 2007).

2.1.2.2 Bipolar Spectrum approach

This research has led to suggestions that there should be a broadening of current narrow DSM-IV criteria to include a "full spectrum" of bipolar disorders (Ghaemi et al., 2001 and 2002; Akiskal et al., 2006; Camacho et al., 2005 and Berk et al., 2006), with a much larger overlap with UMDD than hitherto recognized. Ghaemi and colleagues have suggested that other types of bipolar illness, apart from

bipolar I or II disorders be lumped together into one category, namely bipolar spectrum disorder (Ghaemi et al., 2002).

According to Ghaemi and colleagues (2001), specific clues in the history that could indicate a high likelihood of an underlying bipolar spectrum disorder include: antidepressant–induced mania or hypomania, more than 3 recurrent major depressive episodes, psychotic major depressive episodes, a family history of bipolar disorder in first-degree relatives; a history of anti-depressant induced hypomania or mania; atypical depressive symptoms, according to DSM-IV criteria; hyperthymic personality prior to the onset of depression; early age of onset (before the age of 25); and a highly recurrent pattern of illness with brief episodes. These symptoms are also sometimes called the "soft signs" of bipolar disorder (Akiskal et al., 2006). Furthermore, atypical symptoms of depression, including hypersomnia, hyperphagia, fatigue, and sensitivity to rejection, are also regarded by other authors as strong indicators of underlying bipolar disorder spectrum disorder (Berk et al, 2006; Akiskal et al; 2006, and Benazzi, 2005).

Other suggested features of an underlying bipolar disorder have also been postulated to include postpartum onset of depression (specifically with psychotic features), a seasonal pattern, severe premenstrual syndrome, a lack of response to 3 or more adequate antidepressant trials and an abrupt onset and end to an episode (Ghaemi et al., 2001;Berk et al., 2006). Furthermore, it has been suggested that people with the so-called hyperthymic personality share similarities with

hypomania, including tremendous optimism, increased energy, a decreased need to sleep, extroversion, overconfidence and promiscuity (Akiskal et al., 2006).

Akiskal and colleagues have studied the soft signs of bipolar depression, and suggested that the current narrow DSM-IV criteria can be broadened to include all spectrums of bipolar disorder (Akiskal et al., 2006). Following this work they believe that in addition to the recognized subtypes of bipolar disorder (I and II), others can be added. Thus, cyclothymic depression should be renamed bipolar II ½ disorder, with the degree of cyclothymia being important in qualifying the distinct and severe form of depression in bipolar II ½. In clinical practice this form of depression is often misdiagnosed as borderline or other personality disorders (Akiskal et al., 2000). Furthermore, bipolar III disorder would include the group where hypomania is associated with antidepressant use (currently not considered a variant of bipolar disorder), particularly when associated with a family history of bipolar disorder. Other suggestions may include bipolar III ½ disorder describing hyperthymic temperament associated with substance abuse, and bipolar IV disorder referring to hyperthymic temperament only (Akiskal et al 2006). Of these suggestions, the one with the greatest support is bipolar II ½ disorder as it appears to be the most prevalent and severe expression of the bipolar spectrum and has been suggested to account for a third of all cases of major depressive disorder (Akiskal et al., 2006).

Interestingly, these authors (Akiskal et al., 2006) have also suggested that combining the hard bipolar I and II disorder with the soft bipolar spectrum disorders may account for 65% of major depressive episodes, making it more prevalent than major depressive disorder. Although this suggestion has not been widely tested to date, other authors have had similar proposals. Thus, Angst has in the past been a proponent of the theory that mood disorders existed on a continuum (2001). His approach distinguished between hypomania (m), mania (M), mania with mild depression (Md), mania and major depression (MD), and major depression and hypomania (Dm). He has also provided evidence for brief hypomania, being sub-threshold to DSM-IV criteria for hypomania, and lasting as little as 1-3 days. Given this, he has previously argued that the current diagnostic criteria for bipolar disorder should be revised (Angst, 2001, 2002, 2006 and 2007).

There has been an additional proposal that the bipolar spectrum should be lumped together to include the entire range of bipolar disorders from classic bipolar I to atypical versions (Muzina, 2007).

In contrast, authors such as Ghaemi and Baldessarini (2007) and Patten (2006) have cautioned against broadening the definitions of bipolar disorder. While mood disorders may indeed exist on a dimension, or spectrum, Ghaemi and Baldessarini argue for explicit definitions and rigorous research to allow accurate definition of a bipolar spectrum. Otherwise, it could have the same fate as broad

definitions of major depressive disorder, which they claim are "both unscientific and clinically unworkable" (Ghaemi et al., 2007).

2.1.2.3 Integration of mood and personality

Nonetheless, while a bipolar spectrum disorder approach may be better at explaining the wide clinical nature of these illnesses compared to the limited categorical models, this cannot always explain why theoretically polar opposites can co-exist. Examples that have been cited include depression and mania in mood disorders as well as in aspects of personality, such as compulsivity and impulsivity, and internalizing and externalizing disorders. To try and integrate these approaches, Diogo Lara and colleagues have proposed a model that integrates the spectrum of mood, behavioral disorders and personality disorders (Lara et al., 2006). They - like others – have argued that the categorical approach of the DSM-IV and ICD-10 (where mood, behavioral disorders and personality disorders are represented as distinct entities) are too narrow, and additionally that they do not consider comorbidities as an important part of the diagnostic approach. They also suggest that sub-threshold symptoms have been excluded by such an overly categorical approach. They have therefore proposed a bi-dimensional model based on fear and anger traits. In this they have expanded on the previous work of Cloninger where a mono-dimensional model was described with the extremes (high or low) of two behavior traits, namely "harm avoidance" and "novelty seeking" (Cloninger et al., 1993). Lara and colleagues have also argued that fear and anger traits could provide a basis for understanding the relationship of anxiety disorders, depressive mood disorders, bipolar disorders,

attention-deficit/hyperactivity disorder, alcohol and substance use disorders, other impulse control disorders, as well as personality disorders (specifically cluster B and C disorders). Furthermore, they claim that their heuristic model could explain comorbidities, family history, and course of illness. (Lara et al, 2006). Nonetheless, despite the potential interest in such an explanation, at this time there is little empirical evidence to support this approach.

2.1.2.4 Definitions according to symptomatology

Taken together, it is clear that for a number of reasons the current narrowly defined diagnostic criteria for bipolar I and bipolar II disorders may not adequately capture the full range of symptomatology experienced by patients. This has led to other alternative approaches at defining mood disorders. Mayberg has suggested one of these.

As with others previously mentioned, Mayberg and colleagues have also claimed that the DSM-IV has not allowed room for the phenomenological complexity of mood disorders (Holtzheimer and Mayberg, 2008). An example they use to illustrate this is where two totally different presentations are seen among patients that nonetheless both fulfill criteria for a major depressive disorder. Thus, depressed patients with melancholic features could have a sleep disturbance with insomnia and early morning awakening, loss of appetite, and profound anhedonia, without mood reactivity. In contrast, depressed patients with atypical features could present with a sleep disturbance with hypersomnia, an increase in appetite,

and mood reactivity. Nonetheless, both patients, who have diametrically opposed symptoms, are still considered as having major depressive disorder according to DSM-IV criteria. This led Mayberg, as a neurobiologist studying depressive mood states, to propose a symptom-specific approach. According to her, such an approach can be particularly useful when studying neuroanatomical correlates of sad mood. Different symptoms could be studied including mood and affect, interest and motivation, sleep, appetite, psychomotor activity, emotional bias, and cognition, where changes in a specific symptom could illustrate changes in very specific neuroanatomical regions. This approach has also led to the proposal of a neural network model of mood disorder (Holtzheimer and Mayberg, 2008).

Nevertheless, while these proposed models are of interest, and may provide avenues for future research, most research that will be reviewed in this thesis has been based on the categorical approach outlined in the DSM-IV. Indeed, researchers have argued that constraining broad criteria in bipolar spectrum literature would be essential to ensure progress in future random controlled studies (Ghaemi et al., 2007).

2.2 COURSE AND PROGRESSION OF BIPOLAR DISORDER

Bipolar disorder is a chronic condition, and there are multiple factors that may affect its course and chronicity, as well as how accurately it is diagnosed. These include the symptom pattern, length of illness and age of onset. All of these

factors, and others can affect accuracy of diagnosis and measured frequency in the population.

It is important to note that chronicity without complete remission is highly prevalent in bipolar disorder. Thus, in a long-term naturalistic study (Judd et al., 2002), it was found that bipolar I disorder patients were symptomatically ill 47% of the time. During the time they had symptoms they were 3 times more likely to be depressed than manic, and five times more likely to be depressed than having a mixed episode. Among patients with bipolar II disorder, patients spent 36 times more days depressed than hypomanic and were symptomatically ill 57% of the time. Depressive mood states in both bipolar I and bipolar II disorder are also believed to be more disabling than the presence of a hypomanic or manic episode (Judd et al., 2003 and 2005). In fact, bipolar depressed patients are symptomatic half the time, and days spent each year in a depressed state have been found to be 121 days versus 40 days in a manic or hypomanic state (Post et al., 2005). Thus, there is good evidence that patients with bipolar disorder spend a large part of their lives in a depressed state. Despite this, research into bipolar depression remains very limited.

In terms of longer-term outcome, more than 90% of patients having a single manic episode will have future depressive episodes (APA Guidelines, 2002). Of these manic episodes, 60-70% occur immediately before or immediately after a depressive episode (APA Guidelines, 2002).

Poor or under-diagnosis of bipolar disorder remains an issue, and only 20% of all patients with bipolar disorder are initially correctly diagnosed in the community. Furthermore most of those patients that were initially correctly diagnosed were not treated adequately. They usually received an antidepressant but without also receiving a mood stabilizer, thus increasing the risk of precipitating a manic episode (Suppes et al., 2005). Furthermore, according to the survey by the National Depressive and Manic-Depressive Association carried out in the year 2000, at least 60% of patients with bipolar disorder had previously been diagnosed as UMDD (Baldassano et al., 2006).

It is also possible that the clinical course can predict response to medications. Thus, Ghaemi and colleagues (2002) have argued that clinical and genetic data actually suggests two different response groups. Bipolar 1 disorder or classic manic-depressive illness (also called Cade's Disease named after the discoverer of lithium as a therapeutic agent, John Cade) is characterized by pure manic and pure major depressive episodes with euthymic intervals. This group has an excellent lithium response rate. The less responsive group (bipolar II disorder, cyclothymic disorder, and bipolar spectrum disorder) is regarded to be more common, although just as severe in terms of depressive symptoms. Of these groups, it is likely that the bipolar spectrum disorder group is most widely missed in clinical practice (Ghaemi et al., 2002).

In terms of its chronicity, bipolar disorder is a lifelong illness with numerous episodes and a variable course as well as residual symptoms in up to 30% of patients on adequate treatment (Post, 2005). The initial episode in both men and women tends to be depressive, hence the difficulty in diagnosis (Suppes et al., 2005). It is actually quite common for a patient to have numerous episodes of depression before a manic episode occurs. People with a depressive episode tend to have more insight into their illness and therefore tend to seek treatment sooner. However during a hypomanic or manic episode patients very seldom recognize the impact of their illness on their functioning, and therefore fewer patients seek psychiatric help during this phase (APA Guidelines 2002). Patients have reported that receiving the correct diagnosis of bipolar disorder instead of UMDD can take as long as 10 years (Angst, 2007).

In general, most authors have not found differences in the symptom profile for patients presenting with depressed mood between those who have UMDD and those who have bipolar depression (Mantere et al., 2006).

However, some authors have noticed differences. Thus, in a French multicenter study (EPIDEP) the following key characteristics of bipolar II disorder were noted to be present: at their index depressive episode patients may have a distinct presentation with an overrepresentation of suicidal thoughts, guilt feelings, depersonalization-derealization, hypersomnia and weight gain (Akiskal et al., 2006). In contrast, in unipolar depression there was an overrepresentation of

'psychic" anxiety and initial insomnia. Additionally, Allilaire and colleagues (2001) report a different course of illness for bipolar II disorder, with a younger age of onset of the first depressive episode, a higher rate of suicide attempts and frequent hospitalizations. Nonetheless, as previously mentioned, there is great difficulty in correctly diagnosing bipolar II disorder, and this was mirrored in the EPIDEP study (Akiskal et al., 2006) where only a half of patients received a correct initial diagnosis. This study also found complex dysregulations in temperament in bipolar patients. Specifically, cyclothymic, hyperthymic, and irritable traits were overrepresented. Bipolar disorder probably affects a variety of life experiences, but this doesn't seem to relate to the subtype of bipolar disorder in the way that would be anticipated (i.e. bipolar I disorder having a greater effect than bipolar II disorder). Thus, in an Italian study comprising of 253 patients, euthymic patients with bipolar II disorder actually had a poorer quality of life than euthymic bipolar I disorder (Maina et al., 2007).

Age of onset may also be a factor in severity. Early onset (defined as before age 15) of bipolar disorder has been associated with the most severe form of the illness (Schurhoff et al., 2000). Patients in this group had more psychotic features, greater comorbidity with panic disorder, and poorer lithium response than late onset bipolar disorder (defined as 40 and over). According to Almeida early versus late onset bipolar disorder was associated with lower socio-economic status, a higher frequency of mixed affective episodes, other mood disorders, schizoaffective disorders and schizophrenia (Almeida et al., 2002). Possible age

effects among inpatients with bipolar depression have also been studied. One study found that that older patients that were hospitalized for the first time, especially those older than 65, had more depressive episodes with psychotic features than younger patients (Kessing, 2006). Younger patients (defined in his study as younger than 50) presented more with psychotic manic episodes. No age difference was detected in an outpatient setting. Findings from both these groups suggest that age of onset and hospitalization may be relevant to course and outcome. The mean age of onset of the first manic/hypomanic or major depressive episode has been found to be 18 years for bipolar I disorder, 20 years for bipolar II disorder and 22 years for patients with sub-threshold bipolar disorder (Merikangas et al., 2007). Reasons for any putative age effects are uncertain, but it is possible that an earlier onset implies greater underlying neuropsychiatric changes (Chang et al., 2000).

2.3 INCIDENCE AND PREVALENCE OF BIPOLAR DISORDER

As will be seen, there is a large range in the estimates for the prevalence of bipolar disorders. This varies significantly between studies; part of this may be explained by increasing evidence that high prevalence rates of bipolar spectrum disorders are found in what had previously been considered UMDD patients only.

Several studies suggest that the lifetime prevalence for bipolar I disorder ranges from 0.4% to 3.3 %, while the prevalence rates for bipolar II disorder are

estimated to be between 0.5% - 1.6% (DSM-IV, 2000; Schaffer et al., 2006; Hirschfeld et al., 2003; Ghaemi et al., 2002). In a recent Canadian study, the lifetime prevalence of bipolar disorder (both type I and type II) in Canada was estimated to be 2.2% (Schaffer et al., 2006). A lifetime presence of an anxiety disorder, and the current presence of a substance use disorder, was each significantly associated with the presence of a diagnosis of bipolar disorder. Other measurements that were also significantly associated with bipolar disorder, included a younger age of onset, and low-income (Schaffer et al., 2006). According to Hirschfeld and colleagues (2003) the prevalence for bipolar I and II disorder combined may be as high as 4% in the US.

In keeping with these higher prevalence rates, results from the US National Epidemiological Survey on Alcohol and Related conditions suggest that the lifetime prevalence for bipolar I disorder were 3.3% in this large study (Grant et al., 2005). While this study found no gender differences among patients, the odds of having bipolar I disorder were significantly higher among Native Americans, younger adults, and those that were single (widowed, separated, or divorced) or of lower socioeconomic status. Men were more likely to have unipolar mania (with no recorded episodes of UMDD), and were also more likely to have an earlier onset and longer duration of manic episodes. Women, on the other hand, were more likely to have mixed and major depressive episodes (Grant et al., 2005). Looking at gender differences, Benazzi (2000) could not find significant differences in clinical presentation between males and females with bipolar II

disorder. Nonetheless, there was a tendency for earlier onset of symptoms in females, with more atypical features than among males in his outpatient study. Thus, given that previous research has consistently shown an approximate 2:1 ratio in the frequency of UMDD in females compared to males, further research is needed to clarify whether or not there are differences in frequency of bipolar II disorder between males and females. Interestingly, in a recent study gender-specific lifetime prevalences for males and females have been estimated to be 0.8% and 1.1 % for bipolar I disorder, and in bipolar II disorder the lifetime prevalence for males were 0.9% versus 1.3% for women (Merikangas et al., 2007). In the same study, Merikangas and colleagues found a lifetime prevalence rate of 2.6% in men and 2.1% in women with sub-threshold bipolar disorders.

2.4 PREVELANCE WHEN MEASURING BIPOLAR SPECTRUM DISORDERS

Akiskal and Benazzi (2005) studied 563 consecutive outpatients with a confirmed history of major depressive disorder. They applied less strict criteria for a hypomanic episode, using a duration of 2 days and more, instead of the DSM-IV criteria of at least 4 days. According to their redefinition of hypomania, they found that a substantial amount of their patients (57%) fulfilled their broad criteria for bipolar II disorder. According to these authors, it would be crucial to obtain collateral information, especially about behavioral activation with euphoria and or irritability. Others have also studied groups of patients using different diagnostic criteria for hypomania, leading to a so-called "bipolar spectrum" disorder. Studies

including such patients have estimated prevalence rates of bipolar disorder to be as high as 7% (Ghaemi et al., 2002) and even 8% (Angst 2007).

Merikangas and colleagues (2007) have estimated the lifetime prevalence for sub-threshold bipolar disorder to be 2.4%. In their article sub-threshold bipolar disorder was defined as recurrent hypomania without a major depressive episode or with fewer symptoms than required for hypomania and depression. They also stressed that sub-threshold symptoms were clinically significant and under detected in clinical settings. They have also urged the importance of defining criteria for sub-threshold bipolar disorder in a strict and uniform manner (Merikangas et al., 2007). In this large study, comprising of 9,282 participants, the lifetime prevalence rate was 1.0% for bipolar I disorder and 1.1% for bipolar II disorder, while it was 2.4% for sub-threshold bipolar (Merikangas et al., 2007).

Many of the existing research therefore suggest that the prevalence of bipolar disorder may be greater than past estimates, and furthermore, that the bipolar spectrum disorder group may be the largest of the three groups. Much of the bipolar spectrum disorder group has previously been misdiagnosed as having unipolar major depression. These suggestions will be examined in the present study.

2.5 MISDIAGNOSIS AND OVERLAP BETWEEN MAJOR DEPRESSIVE DISORDER AND SUB-THRESHOLD BIPOLAR DISORDER

One of the recurring themes throughout this thesis is the difficulty of diagnosing bipolar disorder and the overlap between unipolar major depressive disorder (UMDD) and both bipolar disorder and sub-threshold bipolar disorder. This can lead to patients thought to have UMDD subsequently being re-diagnosed. Thus, in a large Polish outpatient study by Kiejna and colleagues (2005), bipolar I disorder was diagnosed in 19.5% of outpatients who initially had a diagnosis of UMDD, and 35% of the UMDD group fulfilled criteria for a bipolar II disorder diagnosis. These authors also determined the incidence of bipolar spectrum disorder, as defined by Ghaemi and colleagues (2001), and diagnosed this in a further 12.6% of their major depressive disorder patients. Thus, in this sample, a majority of patients who were considered UMDD were re-diagnosed as having some type of bipolar disorder.

Data from the Kansas 1500 retrospective study (Othmer et al., 2007) also revealed a lifetime incidence of mania in 27% of a large outpatient group of what had been considered as UMDD patients. This group reported three strong indicators for mania including psychotic symptoms, a family history of mania, and an early onset of symptoms of depression before the age of 25 (Othmer et al., 2007).

In conclusion, it is conceivable that the concept of bipolar spectrum disorder, as defined by Ghaemi and colleagues, could be a viable approach in clinical

psychiatric practice. It could delineate a wider group of patients suitable for treatment than current approaches. Further studies are needed to clarify criteria definitions, and duration of symptoms. Part of the goal of the current thesis is to examine this aspect further, and we examine the frequency of bipolar disorder using both DSM-IV criteria as well as the frequency of bipolar spectrum disorders, using the criteria of Ghaemi and colleagues in our study population.

3 COMORBIDITY OF BIPOLAR DISORDER

While bipolar disorder is often thought of as a discrete entity, it is estimated that 65% of all bipolar patients have another Axis I diagnosis, with 42% having 2, and 24% of bipolar patients experiencing 3 lifetime comorbidities (McElroy et al., 2001). Thus, it is important to realize that for bipolar disorder patients, psychiatric comorbidities are the rule rather than the exception. In fact having at least 1 comorbidity in their lifetime is highly prevalent across the entire spectrum of bipolar illness, and it was estimated as high as 97% in patients with bipolar I disorder, 95% in patients with bipolar II disorder and 88% in patients with sub-threshold bipolar disorder (Merikangas et al., 2007).

Furthermore, as many studies have suggested that many patients with bipolar disorder are misdiagnosed, Baldassano (2006) has suggested that one should look at those misdiagnoses and also regard them as comorbid conditions. In other words, where newly diagnosed bipolar disorder patients were previously diagnosed as having an anxiety disorder or substance use disorder as their main Axis 1 DSM-IV diagnosis, those prior diagnosis should be viewed as comorbid conditions. To date, this proposal has not been substantiated by research.

In terms of recognized conditions occurring comorbidly, Vieta and colleagues (2000) found that anxiety disorders, alcohol and substance use disorders, and personality disorders were common comorbid conditions in bipolar patients. In a

study by McElroy and colleagues (2001) no differences in comorbidity were found between patients with bipolar I and II disorder. In their study they found that an earlier onset of bipolar disorder, more severe episodes and cycle acceleration were significant indicators of current and lifetime comorbidities.

Other researchers also found no significant difference between bipolar I and II disorders in regards to comorbidities. Thus, in a Finnish study with 350 patients (Mantere, et al., 2006) bipolar I and II disorders appeared to differ little in terms of overall comorbidities. Anxiety disorder was comorbidly present in 57%, and there were less cluster A and B comorbidities in this group. Single cluster B (borderline) personality disorder was present in 31%. Eating disorders and somatoform disorders were more prevalent in patients with bipolar disorders. The same group also examined differences in Axis I and II comorbidities between patients with major depressive disorder and bipolar I and II disorders (Mantere et al., 2006). This study showed that UMDD and bipolar disorder patients differed significantly in terms of Axis I and II comorbid disorders. There were more overall comorbidities among patients with UMDD, with more anxiety disorders being diagnosed among the major depressive group (69%) as well as more cluster A (19%) and cluster C personality disorders (32%).

Given the findings from these studies, it is important to consider the current data regarding the prevalence of a variety of different comorbid conditions in bipolar disorder, including anxiety disorders, attention-deficit/hyperactivity disorder

(ADHD), eating disorders, alcohol and substance use disorders, personality disorders, as well as frequency of medical comorbidity with conditions such as the metabolic syndrome. Most of these possible comorbidities are also examined in the present study.

3.1 ANXIETY DISORDERS

The comorbidity of bipolar disorder with different anxiety disorders, including generalized anxiety disorder, posttraumatic stress disorder, panic disorder, with or without agoraphobia, social anxiety disorder, and obsessive-compulsive disorder have been studied.

Simon and colleagues (2004) studied data from a large study in bipolar patients, STEP- BD ("Systematic Treatment Enhancement Program for Bipolar Disorder"). They found that about half of bipolar patients (53% of bipolar I and 46% of bipolar II) have experienced an anxiety disorder during their lifetime. Having an anxiety disorder also increased the lifetime risk for suicide attempts. Thus for posttraumatic stress disorder this risk was 75%, while for those with a comorbid diagnosis of panic disorder with or without agoraphobia the lifetime risk for suicide attempts was 72%. It was somewhat lower in patients with other anxiety disorders: for patients with generalized anxiety disorder the suicide risk was 62%; in those patients with social anxiety disorder, it was 61%, and for obsessive compulsive disorder, the risk was 56%.

Merikangas and colleagues reported lifetime comorbid anxiety disorders in 86% of patients with bipolar I disorder, 89% of patients with bipolar II disorder and 63% of patients with sub-threshold bipolar disorder (Merikangas et al., 2007). It is important to screen for comorbid psychiatric conditions in patients with bipolar disorder, as it is significantly associated with suicidal ideation (74%) and suicide attempts (45%) (Vieta et al., 2000).

Alcohol and substance abuse disorders are common among patients with bipolar disorder (see subsequent discussions). However, STEP-BD data illustrated that in the presence of an anxiety disorder, the rate for alcohol dependence doubled (Simon et al., 2004), and thus it appears that one comorbidity may increase the prevalence of another.

Baldassano and colleagues (2005) looked at gender difference between the first 500 participants in STEP-BD. They found that apart from posttraumatic stress disorder, which occurred more frequently in women than men (21% versus 9%), there were no gender differences for other comorbid anxiety disorders.

It is therefore clear that the presence of a comorbid anxiety disorder with bipolar disorder is clinically very significant. In addition, having any anxiety disorder also predicted a shorter time spent in a euthymic state, as well as an earlier onset of illness (Merikangas et al., 2007).

Others have also suggested that such a comorbidity can have additional implications. Thus, according to Keller (2006) an anxiety disorder in the presence of bipolar disease could predict difficulties in pharmacological management due to poor treatment response to lithium and anticonvulsants.

In this thesis we have examined how frequently anxiety disorders are comorbid with bipolar disorders in our study population.

3.2 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD).

There have long been suggestions that patients with ADHD may be more likely to subsequently develop bipolar disorder, but this association is not clear (Sachs et al., 2000). However, making the correct diagnosis in this population has been notoriously difficult due to a large overlap of symptoms (Berk et al., 2006). According to these authors, in young people with bipolar disorder higher rates for mixed mania and rapid cycling may be present, which could aid differentiation. Examining this systematically in the first 1,000 participants of the STEP-BD study, Nierenberg and colleagues (2005) found that 9.5% had a lifetime diagnosis of ADHD. Thus, in their lifetime almost 1 in 10 bipolar patients had ADHD as a child. As a comorbid condition ADHD predicted an earlier onset of bipolar disorder, especially bipolar I disorder. This association appeared to be stronger in males. Having ADHD as a comorbid condition also predicted the presence of other comorbidities. Thus, there was a significant comorbidity with agoraphobia,

social anxiety disorder, posttraumatic stress disorder, and generalized anxiety disorder. Alcohol and substance abuse was another comorbid risk of ADHD. Among patients with ADHD, the risk for the above mentioned comorbid conditions doubled. Consistent with this, Hirshfeld-Becker and colleagues (2006) found that the offspring of parents with bipolar disorder had a higher rate of ADHD and bipolar disorder.

Overall, therefore, there appears to be a significant comorbidity and shared risk between patients with ADHD and those with bipolar disorder. Further research to clarify this relationship is needed (Chang, 2000).

Given these possible links, in the present study we have examined how frequently patients in our sample had a diagnosis of ADHD as a child, although it is recognized that a lack of a diagnosis retrospectively does not fully exclude that an individual may have met diagnostic criteria when younger.

3.3 EATING DISORDERS.

According to STEP-BD data, 12% of women had a comorbid bipolar disorder and eating disorder, specifically bulimia nervosa. In comparison, the comorbidity rate in men was only 1.6%, which almost certainly reflects the low prevalence rates of eating disorders in males. The authors concluded that this rate does not significantly differ from the general population (Baldassano et al., 2005).

However, McElroy and colleagues (2005) found a relationship between bulimia nervosa and bipolar II disorders. More specifically, there was an association between sub-threshold bipolar symptoms and eating disorders in adolescents, and between binge eating and hypomania in adults. Nonetheless, overall it remains uncertain if there are any significant relationships between bipolar disorder and eating disorders. We have not examined the presence of eating disorders in our adult population.

3.4 ALCOHOL AND SUBSTANCE USE DISORDERS.

Most studies on substance abuse comorbidities in patients with bipolar disorder have found that both disorders occur comorbidly, but the range has been large, varying from 17% to 64%. According to STEP-BD study the prevalence rate was 37% (Baldassano 2006). In a review article, Baldassano (2006) stated that patients with bipolar disorder had the second highest lifetime comorbid risk for alcohol abuse and dependence (46% in bipolar I and 39% in bipolar II disorders). In comparison, the rate among patients with major depressive disorder was 17%. Only patients with antisocial personality disorder had a higher rate of 74%. Grant and colleagues (2005) found a lifetime prevalence of 58% for any alcohol use disorder and 38% for any drug use disorder among patients with bipolar I disorder. The lifetime prevalence for nicotine dependence among patients with bipolar I disorder was 44%. Patients with cocaine dependence were more likely to have bipolar I disorder than bipolar II disorder, and were also more likely to have

comorbid antisocial personality disorder (Mitchell et al., 2007). Comorbid alcohol dependence was more likely to co-occur with generalized anxiety disorder in bipolar II disorder. For bipolar II disorder any substance use disorder was as high as 40%. In patients with bipolar I disorder this rate was 60%, where it was 35% in patients with sub-threshold bipolar disorder (Merikangas et al., 2007).

In conclusion, while it is clear that patients with bipolar disorder have a high rate of comorbidity with drug and alcohol abuse, it remains uncertain if this is due to patients with bipolar disorder demonstrating higher risk-taking behavior, possibly due to a manic or hypomanic state, or alternatively may represent an underlying common etiological factor. To help further understand possible relationships we have examined comorbidity of substance use disorders in the present study.

3.5 COMORBID PERSONALITY DISORDERS.

Grant and colleagues (2005) examined comorbidity rates between bipolar I disorder and 7 personality disorders (avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorders). They found that avoidant, dependent, and paranoid personality disorders were the most strongly related.

In a small Japanese study (Utsumi et al., 2006), a high comorbidity between bipolar disorder patients and borderline personality disorder was found (6 out of

15 patients). In addition Akiskal has proposed the presence of a subgroup of patients with borderline personality disorder where risk genes for bipolar disorder may lead to a joint presentation of both illnesses (Akiskal, 2006). He also suggested that mood lability was the strongest predictor of hypomania. Benazzi has supported this view, and in a study (2006) he found that the borderline trait of "affective instability", but not "impulsivity" was associated with bipolar disorder. In contrast, others have argued against broad statements that viewed borderline personality disorder as a variant of bipolar disorder (Stone, 2006; Gunderson et al., 2006), suggesting that when borderline personality disorder co-occurred with bipolar disorder this might represent an interaction between biological and environmental factors.

Nonetheless, there does seem to be the possibility of a more specific overlap between bipolar disorder and borderline personality disorder. Thus, in a study by Gunderson and colleagues (2006), 196 patients with borderline personality disorder, and 433 with other personality disorders (schizotypal-, avoidant-, and obsessive compulsive disorder) were followed up over 4 years. Of the patients with borderline personality disorder, 19% also had bipolar disorder. For the other personality disorders in this study, only 8% also had bipolar disorder. Furthermore, 8% of patients with borderline personality disorder developed new onset bipolar disorder every year, which was higher than in patients with other personality disorders. The authors concluded that there might be a modest association between borderline personality disorder and bipolar disorder. The

reverse situation, namely whether borderline personality disorder occurred as a subsequence in bipolar disorder patients has also been studied by Gunderson and colleagues (2006). They found a somewhat higher tendency to manifest borderline personality disorder, but again reiterated that there was only a modest discernible link.

Paris and colleagues (2007) suggested that available data failed to support a conclusion that borderline personality disorder and bipolar disorder exist on a continuum or spectrum. However, they have suggested that etiologies for both could be overlapping. To help clarify differences between these conditions Magill (2004) has stressed the importance of obtaining a thorough longitudinal history. In the present study we have determined the frequency with which patients with bipolar disorders also had a personality disorder.

3.6 MEDICAL COMORBIDITIES: SYMPTOMS CONSISTENT WITH THE METABOLIC SYNDROME

Patients with schizophrenia and affective disorders have been shown to have an increased risk of death from medical causes and a lifespan that can be up to 20 years shorter in comparison to the general population (Newcomer, 2007). The reason for this remains uncertain, but one possibility is that there may be an increased risk of medical comorbidity in these populations, possibly involving the metabolic syndrome. Metabolic syndrome includes patients who develop obesity, insulin resistance, dyslipidemia, impaired glucose tolerance, and hypertension. Of

these five major features, the presence of three or more have been regarded as diagnostic of the metabolic syndrome (Newcomer, 2005). This syndrome has also been shown to be an important risk factor in the development of both type 2 diabetes mellitus and cardiovascular disease. However, a complication arises from the effects of medications (see below), and thus it remains uncertain whether an increased propensity to develop metabolic syndrome in bipolar patients is due to intrinsic factors or to medications given to treat the condition.

Atypical antipsychotics have been frequently and effectively used in the pharmacological management of bipolar disorder as suggested by the leading independent treatment recommendation body in Canada, the Canadian Network for Mood and Anxiety Disorder Treatments (CANMAT, 2005 and 2006). They have been found to be as effective as established drug therapies in treating both phases of the illness when compared to placebo (Derry et al., 2007). However, treatments with the atypical antipsychotics have shown clear evidence of metabolic risks as a result of using these medications in a recent large study-Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE; McEvoy et al., 2005). In particular, clozapine and olanzapine have been shown to produce substantial weight gain and associated metabolic syndrome, while in contrast, risperidone and quetiapine produced intermediate changes in mean weight in comparison to treatment with other atypical antipsychotics, and discrepant results in regards to metabolic risk. Among currently available atypical antipsychotic medications, only aripiprazole and ziprazodone induced the lowest mean change

in weight gain and had no effect on risk for metabolic changes (Newcomer. 2007). Unfortunately neither aripiprazole nor ziprazodone are available in Canada. It is of note that a combination of olanzapine (with fluoxetine) has been included as suggested second-line treatment strategies by CANMAT (2005).

The current clinical and epidemiological data have suggested that apart from clozapine, antipsychotics rarely increase blood pressure directly. However as a group antipsychotics increased obesity and hyperlipidemia, and could therefore indirectly increase blood pressure. It has been postulated that olanzapine and clozapine may interfere in a direct way with blood pressure in a yet unknown manner, apart from their effect on obesity. Low potency antipsychotics, as well as clozapine, olanzapine and possibly quetiapine have been linked causatively to dyslipidemia, apart from their effect on obesity (de Leon et al., 2007).

However, while there are clear risks from atypical antipsychotics, the reverse situation, where medical illness has been associated with psychiatric illness, has also been found. Thus obesity has been associated with a shorter time to depression recurrence in bipolar I disorder (Fagiolini et al., 2003). In a recent study there was an increased risk among obese women for bipolar I disorder, accompanied by atypical depressive episodes (Pickering et al., 2007).

Taken together, therefore, these data suggest strongly that there is a substantial medical risk to the patient associated with these, albeit efficacious, drugs. Of note

is that CANMAT criteria have recently been updated to include olanzapine, quetiapine, lithium, and lamotrogine for use in bipolar depression (Yatham et al., 2006).

Given these potential risks, and the higher use of atypical antidepressants in bipolar disorder patients, we have looked at risk factors for metabolic syndrome among the various patient groups.

3.7 SUICIDE

Among the first 500 participants of the STEP-BD study (Simon et al., 2004) it was found that about half of them experienced a lifetime anxiety disorder. STEP-BD data also showed that bipolar disorder patients have a higher suicide risk when an anxiety disorder is present (Simon et al., 2004). In this study, 60% of bipolar disorder patients with a comorbid anxiety disorder attempted suicide, versus 27% of bipolar patients without a comorbid anxiety disorder. Lifetime rates for suicide attempts were 52% in bipolar patients with any anxiety disorder and 22% in those without an anxiety disorder (Simon et al., 2004).

A Finnish study by Valtonen and colleagues (2005) found that over their lifetime 80% of patients with bipolar disorder exhibit suicidal ideation or ideation plus suicide attempts. In this study, comprised of a total of 191 inpatients and outpatients, no difference in prevalence for suicidal behavior could be found

among patients with bipolar I or II disorders. Key risk factors included depression with feelings of hopelessness, comorbidity and prior suicidal behavior. This is a very high rate, and suggests a significant risk of suicide in bipolar patients, which is sadly borne out in other studies showing that 10-15% of bipolar patients commit suicide (APA Guidelines, 2002).

The risk for suicide attempts in so-called mixed bipolar depression have been found to be quite high. According to a study by Balazs and colleagues (2006) the authors suggested that irritability and psychomotor agitation were strong predictors for suicide attempts in patients with mixed bipolar depression, especially with a bipolar II disorder diagnosis.

Simon and colleagues (2007) studied 120 outpatients in the STEP-BD program who had comorbid anxiety disorders. They found that lifetime comorbid anxiety disorder was associated with doubling of the odds for past suicide attempts, where current comorbid anxiety disorder doubled the odds for current suicidal ideation. They have urged that when an anxiety disorder co-occurred in patients with bipolar disorder, it would be prudent and essential to do a careful clinical risk assessment for suicide.

In the current study we did examine this, as a risk for suicide would exclude patients from any of our treatment or imaging studies. Those patients with significant suicidal ideation were referred for further psychiatric management.

3.8 DEFINITION OF ATYPICAL DEPRESSION AND RELEVANCE TO BIPOLAR DEPRESSION

Although not strictly a comorbid condition, the presence of atypical features of depression have been included here as it is possible that there are differences in the frequency of atypical features between patients with UMDD and those with bipolar depression. The concept of atypical depression dates back to the work of West and Dally in the 1950s (Thase, 2007). They described a subgroup of patients who were not responsive to electro-convulsive therapy or the tricyclic antidepressant, imipramine. However, patients did respond to iproniazid, a mono-amine oxidase inhibitor (MAOI). Patients with prominent anxiety and multiple phobias formed part of their work (Davidson, 2007).

In the late 1960s workers in Columbia and others, like Robinson and colleagues, emphasized the concept of vegetative reversal. It was thought that atypical depression was present in younger, nonmelancholic women who had an earlier onset with mainly reverse vegetative symptoms (Thase, 2007). In contrast, other authors such as Liebowitz and Klein coined the term "Hysteroid Dysphoria" in the late 1970s. Their patient population was mainly depressed women who had atypical features, like overeating, oversleeping, and leaden paralysis, and were extremely sensitive to personal rejection (Liebowitz et al., 1979). Nonetheless, currently the reversed vegetative symptoms are considered key and current diagnostic criteria emphasize reverse vegetative symptoms such as overeating, and oversleeping as a part of the current DSM-IV criteria used to specify a

depression as "atypical". The association with anxiety disorders, especially social anxiety disorder, still remains important (Parker, 2007).

In DSM-IV the diagnostic requirements for "atypical" depression are mood reactivity (Criterion A), and the presence of at least two of the following features (Criterion B): increased appetite or weight gain; hypersomnia; leaden paralysis; and a longstanding pattern of extreme sensitivity to perceived interpersonal rejection. These features must predominate during the most recent two-year period (for dysthymic disorder) or the most recent two-week period (for UMDD). When criteria have been met for melancholic or catatonic features during the same depressive episode, the atypical specifier is not given.

Michael Thase (2007) has argued that atypical depression is hardly atypical in the 21st century, as it is one of the most common presentations of UMDD disorder, and probably the predominant subtype in patients who are not melancholic or psychotic. He also suggested that the strongest evidence for the validity of "atypical" depression is that patients meeting the criteria for the specifier have a better response to mono-amine oxidase inhibitors than to tricyclic antidepressants or placebo, implying different neuropsychiatric changes.

There appears to be a relationship between bipolar disorder and atypical depression. In a large study, 198 depressed patients with atypical features and 122 depressed patients without atypical features were compared (Agosti et al., 2001).

In this study those patients with atypical features had a 3.6-times greater prevalence of bipolar disorder, than those without. Interestingly, atypicality predicted an earlier onset and greater functional impairment and a chronic course. Atypical depression has also been associated with Akiskal's soft sign for bipolar depression, and Perugi and colleagues (1998) suggested that 72% of atypical depression patients actually had bipolar spectrum disorder. In another Italian study Akiskal and Benazzi(2005) found that atypical depression occurred twice as often in patients with bipolar II disorder than UMDD (Akiskal et al., 2005). Taking all these studies together, it has been proposed that hypersomnia is relatively specific for bipolar II disorder (Berk et al., 2005).

Given this possibility, and the fact that this possible relationship has been relatively little studied, we have determined the frequency of atypical features of depression in our patient population.

4 STUDY METHODOLOGY FOR ASSESSMENT OF OUTPATIENTS

4.1 DEFINITION OF SAMPLE

The "Mood disorder Clinic" at the Department of Psychiatry in the University Hospital in Edmonton came into being in May 2004 and operated for 3 years until April 2007. Dr. P.H Silverstone and the writer jointly ran this research clinic. It operated on Fridays during normal working hours.

The clinic's primary purpose was to accurately diagnose and treat patients referred by a family physician, who in most cases had a poorly responsive mood disorder. In addition, patients who came to this clinic were assessed for suitability and eligibility for clinical research studies in mood disorder, including those that form the basis of this thesis. In this clinic patients were usually seen within two to three weeks after referral. Letters were sent to approximately 80 family physicians inviting them to refer patients to the mood disorder clinic, with all physicians being made aware of the research nature of the clinic, and this also being re-iterated to patients both before they arrived and during their visit. We were particularly interested in recruiting depressed patients who general practitioners had difficulty in managing pharmacologically, who were treatment resistant, or where physicians were not sure whether the diagnosis was that of a major depression or bipolar depression. We requested that general physicians refer patients who were not previously on medication for psychiatric problems where

possible. As there are a shortage of psychiatrists in Edmonton and waiting time to be assessed by a psychiatrist was several months, this clinic would also assist family physicians by providing rapid assessment and treatment guidance for patients.

We limited the clinic to adult patients and excluded those who were severely ill or who required admission, as the clinic functioned on an outpatient basis. An initial assessment was scheduled for an hour, after which patients were usually referred back to their physicians with recommendations for further management. Some patients who were severely ill, or at risk to themselves or others were admitted as appropriate. Patients whose pharmacological management was more complex were offered brief follow-up visits that was scheduled for 15 minutes and/or referral to other appropriate services. For example, patients who were deemed to benefit from any of the outpatient psychotherapeutic services at the University Hospital were referred to the appropriate clinics. Some patients who did receive a diagnosis of bipolar or unipolar depression were specifically followed up, if they qualified and agreed to other treatment and imaging studies, which did not form part of this thesis.

4.2 METHODOLOGY FOR SCREENING PATIENTS

Patients were clinically assessed according to standard psychiatric clinical practice guidelines using semi-structured interviews and recorded in a

standardized format. All the information was obtained directly from patients, and from referral notes of general physicians. In some cases, family members accompanying patients could provide additional collateral information. The following data was obtained from patient's files and documented for each patient: age, gender, marital status, employment status, reason for referral, prior psychiatric history, family history of psychiatric illness, substance use history, and medical history. After a mental status evaluation was completed a diagnosis according to DSM-IV criteria was made. The data was then tabulated and further analyzed as follows:

4.2.1 *MAJOR DSM-IV AXIS 1 DIAGNOSES.*

The following diagnoses were made:

a. Unipolar UMDD
b. Dysthymic disorder
c. Adjustment disorder with depressed mood
d. Bipolar I disorder, most recent episode depressed
e. Bipolar II disorder, currently depressed
f. Cyclothymic disorder
g. Bipolar disorder not otherwise specified
h. Schizoaffective disorder, depressed type
i. Bipolar I disorder, most recent episode manic
j. Bipolar I disorder, most recent episode hypomanic
k. Bipolar I disorder, most recent episode mixed
l. Panic disorder with agoraphobia
m. Generalized anxiety disorder
n. Posttraumatic stress disorder

o. Obsessive-Compulsive disorder
p. Social phobia
q. Substance induced mood disorder, with depressive features
r. ADHD
s. Delusional disorder: persecutory type
t. V-code occupational problem
u. V-code relational problem not otherwise specified
v. None

These diagnoses were condensed into 5 main groups as follows:

Group 1: UMDD

Group 2: Bipolar depression, where only depressed patients with a diagnosis of bipolar I or II disorder were included. Among these patients there were 4 patients with a diagnosis of bipolar I disorder, most recently depressed, and 58 patients with a diagnosis of bipolar II disorder. We felt that it was appropriate to include the bipolar I patients, although there were only a few, with the bipolar II group, because this group would be representative of DSM-IV definition of bipolar depression.

Group 3: Psychotic disorder, where bipolar I disorder, currently manic or hypomanic were included, as well as schizoaffective disorder, depressed type and delusional disorder.

Group 4: Anxiety disorder, where all the different anxiety disorders were grouped together.

Group 5: All other Diagnosis.

4.2.2 COMORBIDITIES

4.2.2.1 MAJOR COMORBID DSM-IV AXIS I OR II DIAGNOSES

The following diagnoses were made:

a. Generalized anxiety disorder
b. Panic disorder, with or without agoraphobia
c. Social phobia
d. Obsessive-Compulsive disorder
e. Posttraumatic stress disorder
f. Alcohol use disorders (dependence or abuse)
g. Cocaine use disorders (dependence or abuse)
h. Cannabis use disorders (dependence or abuse)
i. Polysubstance-related disorder
j. Borderline personality disorder
k. Cluster C personality disorder (dependent, obsessive-compulsive or avoidant.)
l. Eating disorder
m. Other impulse control disorders
n. V-code stressors
o. None

These were then condensed to 4 groups.

Group 1 included all anxiety disorders.

Group 2 included all substance-related disorders.

Group 3 included personality disorders.

Group 4 included all others.

Although some patients had more than one comorbid psychiatric diagnosis, we only included the most important one.

4.2.2.2 *B. COMORBID MEDICAL PROBLEMS*

The following diagnoses were seen in the patient population, grouped as follows:

a. Hypothyroidism
b. Risk factors for metabolic syndrome (obesity, insulin resistance, dyslipidemia, glucose intolerance, and hypertension)
c. Migraine headaches
d. Gastroenterological diagnosis
e. Cancer
f. Glaucoma
g. Arthritis and other musculoskeletal ailments
h. Fibromyalgia
i. Osteoporosis
j. Asthma
k. Multiple sclerosis
l. Other cardiovascular illnesses
m. None

They were then condensed to 5 groups.

Group 1 included 27 patients who had risk factors for the metabolic syndrome.

Group 2 included 17 patients with neurological illnesses. Please note that 13 patients had a diagnosis of migraine; 3 patients had a diagnosis of multiple sclerosis, and 1 patient had epilepsy.

Group 3 included 28 patients with hypothyroidism

Group 4 included 243 patients without any comorbid medical diagnoses.

4.2.2.3 COMORBID ALCOHOL AND SUBSTANCE ABUSE DISORDERS

The following diagnoses were made:

a. Alcohol use disorders (dependence or abuse)
b. Cannabis use disorders (dependence or abuse)
c. Cocaine use disorders (dependence or abuse)
d. Polysubstance dependence
e. Over the counter medication abuse
f. Opioid-related disorders
g. Nicotine-related disorders
h. None

They were condensed to 4 groups.

Group 1 included all alcohol use disorders (dependence or abuse).

Group 2 included all substance use disorders (dependence or abuse).

Group 3 included all polysubstance dependence.

Group 4 included all other or no diagnoses.

4.2.3 OTHER MEASUREMENTS

4.2.3.1 AGE

Ages among patients varied from 18 to 87, and were defined as follows:

Group 1: 18 to 35

Group 2: 36 to 49

Group 3: 50 to 65

Group 4: > 65

4.2.3.2 GENDER

Group 1: male

Group 2: female

4.2.3.3 EMPLOYMENT STATUS

Group 1: employed.

Group 2: unemployed

Group 3: retired

Group 4: students

4.2.3.4 MARITAL STATUS

Group 1: married

Group 2: never married or single

Group 3: separated or divorced

4.2.3.5 REASON FOR REFERRAL

The following were the primary reasons for referral, grouped as follows:

a. Anxiety attacks
b. Depressed mood or mood swings
c. Mood swings of uncertain origin
d. Psychotic
e. Suicidal
f. For review of medication
g. To have disability forms for unemployment completed
h. To get drivers license reinstated
i. Possible attention-deficit/hyperactivity disorder
j. V-Code stressors (work, family, and relational)
k. Memory loss

They were re-grouped as follows:

Group 1: anxiety

Group 2: depressed mood

Group 3: mood swings of uncertain origin

Group 4: other

4.2.3.6 PRIOR PSYCHIATRIC HISTORY

The following were found:

a. Prior major depressive episodes
b. Prior bipolar I or II disorder diagnosis
c. Eating disorders
d. Generalized anxiety disorder
e. Obsessive-compulsive disorder
f. Social phobia
g. Panic disorder with or without agoraphobia
h. Major depressive disorder with post partum onset
i. Alcohol use disorders (dependence or abuse)
j. Substance-related disorders (dependence or abuse)
k. Attention-deficit/hyperactivity disorder
l. None

They were grouped as follows:

Group 1: prior UMDD

Group 2: prior bipolar I or II disorder

Group 3: prior anxiety disorder

Group 4: prior substance use disorder

Group 5: other diagnoses, including attention-deficit/hyperactivity disorder

4.2.3.7 FAMILY HISTORY OF PSYCHIATRIC PROBLEMS

The following were documented for all patients:

Group 1: any mood disorder

Group 2: any anxiety disorder

Group 3: alcohol and other substance use disorder

Group 4: other

5 DESCRIPTIVE RESULTS FROM ALL PATIENTS INVOLVED IN OUTPATIENT STUDY

We were able to assess 315 consecutive patients during the period the clinic ran, and assessment of these patients forms the basis for this thesis.

5.1 MAJOR AXIS 1 DSM-IV DIAGNOSIS

Patients were categorized according to their primary diagnoses. Of the 315 patients seen at the mood disorder clinic, 249 patients (79.1%) had a primary diagnosis of a depressive mood disorder.

a. UMDD was the primary diagnosis in 187 patients (59.4%) of the total population.
b. Bipolar depression according to DSM-IV criteria was the primary diagnosis in 62 patients (19.7%).
c. Anxiety disorder was the primary diagnosis in 23 patients (7.3%).
d. Psychotic disorder was the primary diagnosis in 12 patients (3.8%)
e. Another primary diagnosis was made in 31 patients (9.8%).

5.2 COMORBIDITIES

5.2.1 COMORBID PSYCHIATRIC DIAGNOSIS

a. Any anxiety disorder was comorbidly present in 88 patients (27.9%) in our sample of 315 patients.

b. A comorbid diagnosis of alcohol and substance use disorder was made in 19 patients (6.0%).

c. A personality disorder was diagnosed in 20 patients (6.3%).

d. Another diagnosis was made in 188 patients.

5.2.2 COMORBID MEDICAL DIAGNOSIS

a. A diagnosis of risk factors for metabolic syndrome was made in 27 patients (8.6%).

b. Any neurological illness was present in 17 patients (5.4%).

c. Hypothyroidism was diagnosed in 28 patients (8.9%).

d. Another medical diagnosis was made in 20 patients (6.3%).

e. There were 223 patients (70.8%) who did not have a comorbid medical diagnosis.

5.2.3 SUBSTANCE COMORBIDITIES

a. Alcohol use disorder was present in 29 (9.2%) of our patients.

b. Substance use disorder was present in 26 of our patients (8.3%).

c. A diagnosis of polysubstance dependence was present in 17 patients (5.4%).

d. Substance comorbidities were absent in 243 patients (77.1%).

5.3 OTHER MEASUREMENTS

5.3.1 AGE

a. 116 patients (36.8%) were between the age of 18 and 35.

b. 103 patients (32.7%) were between the age of 36 and 49.

c. 89 patients (28.3%) were between the age of 50 and 65.

d. 7 patients (2.2%) were older than 65 years.

5.3.2 GENDER

Of the 315 patients in our group, 207 were women (65.7%) and 108 (34.3%) were men.

5.3.3 EMPLOYMENT STATUS

a. 240 of our patients (76.2%) were employed.

b. 52 of patients (16.5%) were unemployed.

c. Retired patients accounted for 16 patients (5.1%).

d. There were 7 students (2.2%).

5.3.4 MARITAL STATUS

a. In the total group, 214 patients (67.9%) were married.

b. 84 patients (26.7%) were never married.

c. 17 patients (5.4%) were divorced or separated.

5.3.5 REASON FOR REFERRAL

a. 218 of our patients (69.2%) were referred because of depressed mood

b. 40 patients (12.7%) were referred because of mood swings of uncertain origin

c. 24 patients (7.6%) were referred because of anxiety.

d. 33 patients (10.5%) were referred for other reasons.

5.3.6 PRIOR PSYCHIATRIC HISTORY

a. 171 of our patients (54.3%) had a prior history of UMDD.

b. 31 patients (9.8%) had a prior history of bipolar I or II disorder.

c. 33 patients (10.5%) had a prior history of anxiety disorder

d. 9 patients (2.9%) admitted to a prior history of alcohol and/or substance use disorder.

e. 71 of our patients (22.5%) had no prior psychiatric history.

5.3.7 FAMILY HISTORY OF PSYCHIATRIC PROBLEMS

a. A family history of any mood disorder was present in 75 patients (23.8%).

b. A family history of alcohol and/or substance use disorder was present in 25 patients (8.0%).

c. A family history of any anxiety disorder was present in 8 patients (2.5%).

d. 207 patients (65.7%) reported no or another family history.

6 DISCUSSION OF THESE RESULTS

It should be noted that the sample size gathered in this study (315 patients) is significant and compares favorably with much of the previously reviewed research. It is also important to note that we followed DSM-IV diagnostic criteria rigorously, and using these criteria 249 patients (79.1%) had either a diagnosis of major depressive disorder or bipolar depression. The primary diagnosis of UMDD was diagnosed in 187 patients (59.4%), while bipolar depression (primarily bipolar II disorder) was diagnosed in 62 patients (19.7%).

In comparing our findings to those of previous studies, which have looked at similar populations, the prevalence of bipolar depression in our group was significantly lower than others, given that other outpatient clinic studies suggested that the rates for bipolar depression were as high as 65% (Akiskal, 2006). One of the reasons for this difference could be in the patient populations, as it can be argued that those figures were obtained in specialized psychiatric patients where only patients with a mood disorder diagnosis were seen and where broad inclusion criteria for bipolar depression were used.

In terms of diagnostic criteria, previous studies using broad criteria have found rates of bipolar II depression to be between 40 and 60% (Akiskal, 2006; Angst, 2006).

As mentioned in the introduction, however, there is some confusion regarding these criteria, in that duration of hypomanic symptoms is anywhere between 1 and 3 days (Angst, 2007; Akiskal et al., 2006; Benazzi, 2005). Also as previously noted, there is no consensus currently for including patients with bipolar spectrum disorder. Nonetheless, since we applied DSM-IV criteria strictly, we believe that the prevalence of bipolar depression was 19.7% in our patient population. It is of interest to note that of those 62 bipolar depressed patients, only 21 patients were previously diagnosed with bipolar disorder, while 32 patients had previously been diagnosed with UMDD. Two patients had a prior diagnosis of an anxiety disorder, one patient had a prior diagnosis of substance use disorder, and 6 patients had another psychiatric diagnosis. Thus, of the total number of patients with definite bipolar depression only one third (34%) were recognized by family physicians as having some form of bipolar disorder. These findings support previous suggestions that a bipolar disorder diagnosis is often misdiagnosed as unipolar major depressive disorder (Angst, 2007; Berk et al., 2005).

7 COMPARISON OF 62 BIPOLAR DEPRESSED PATIENTS WITH 187 UMDD PATIENTS.

7.1 *METHODOLOGY COMPARING 62 BIPOLAR DEPRESSED PATIENTS WITH 187 UMDD PATIENTS.*

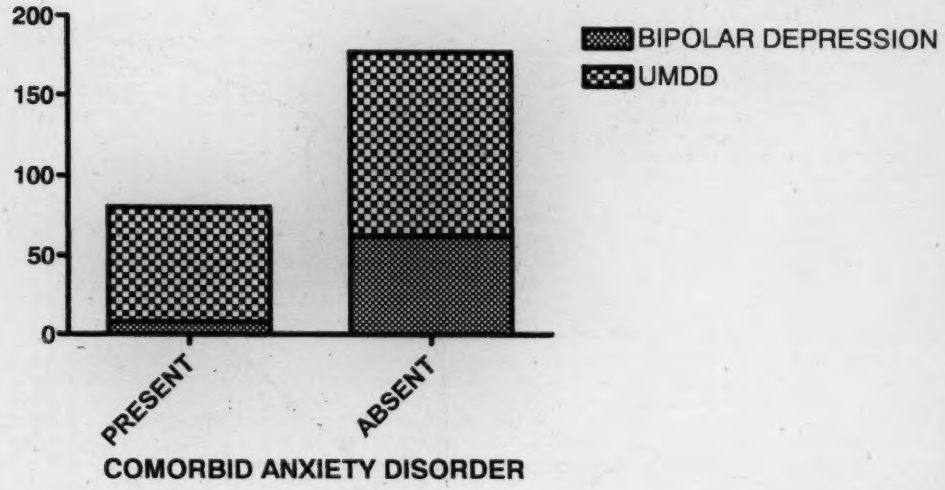
In our sample, bipolar depression was present in 62 patients and UMDD was present in 187 patients. Several comparisons between these two groups were made. Data were entered into contingency tables, and nonparametric Pearson's exact tests with a confidence interval of 95%, were performed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Firstly the different comorbidities present in bipolar and UMDD were compared, namely psychiatric, medical, and substance use comorbidities. Secondly, the other measurements that were documented were compared, namely age, gender, employment status, marital status, reason for referral, prior psychiatric history, and family history.

7.2 RESULTS

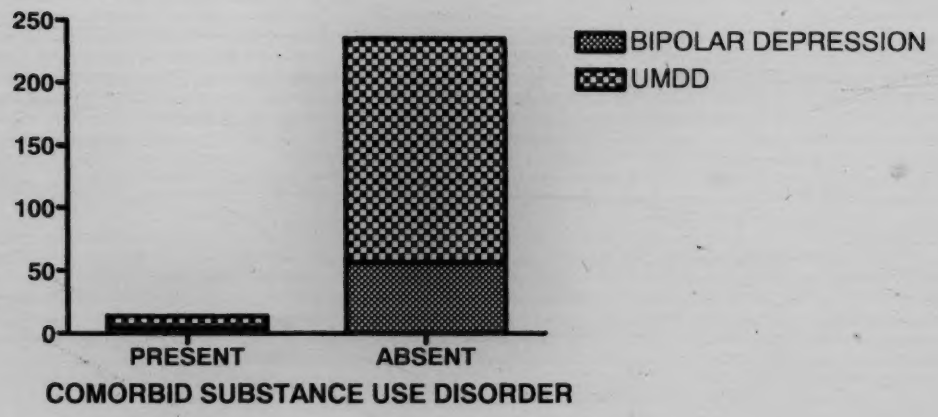
7.2.1 COMORBIDITIES

7.2.1.1 Pearson's exact test comparing bipolar depression and UMDD in regards to comorbid anxiety disorders.



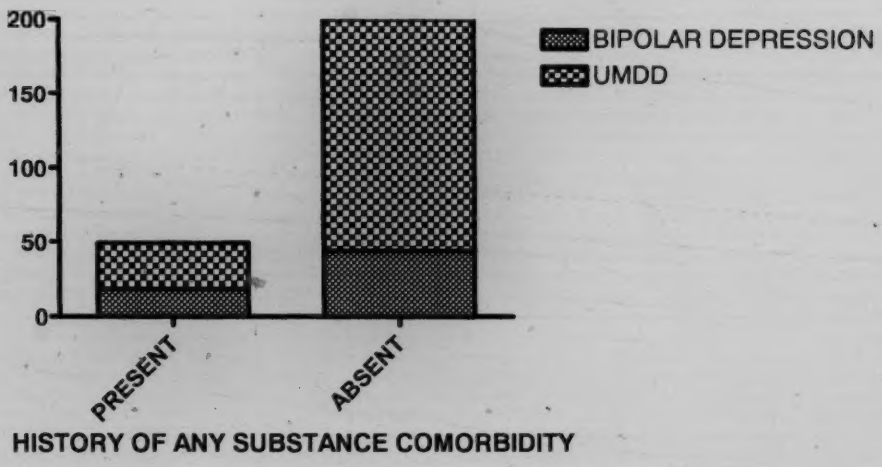
An anxiety disorder co-occurred in 72 patients (38.5%) of the 187 major depression group (UMDD) compared to only 8 patients out of the 62 patients (16.1%) in the bipolar depression group. This difference was considered extremely significant (Chi-square17.4, degree of freedom: 1; two-sided p value: <0.001). Thus, UMDD patients were significantly more likely to have a comorbid anxiety disorder than bipolar depressed patients.

7.2.1.2 Pearson exact test comparing bipolar depression and UMDD in regards to substance use disorder comorbidity.



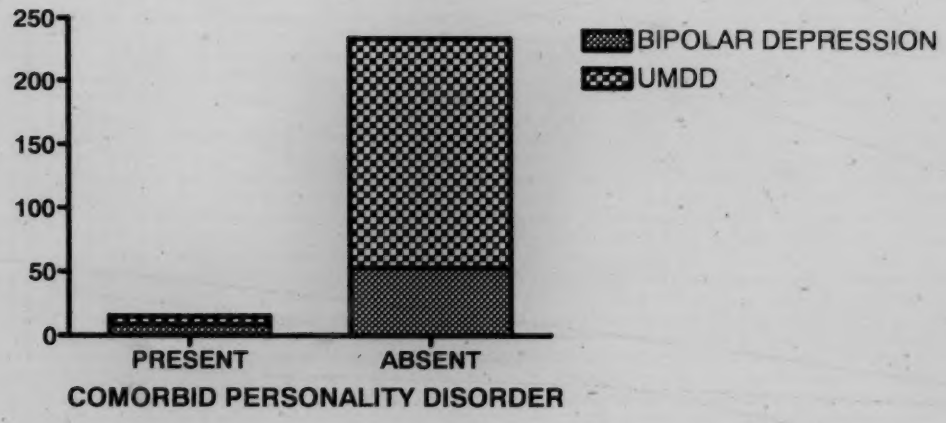
Alcohol and/or any substance use disorder were comorbidly present in 9 of 187 (4.8%) of UMDD patients, and 5 of 62 (8.1%) of the bipolar depression patients, considered a non-significant difference (two-sided p value =0.346).

7.2.1.3 Pearson's exact test comparing bipolar depression and UMDD in regards to a history of any substance use disorder.



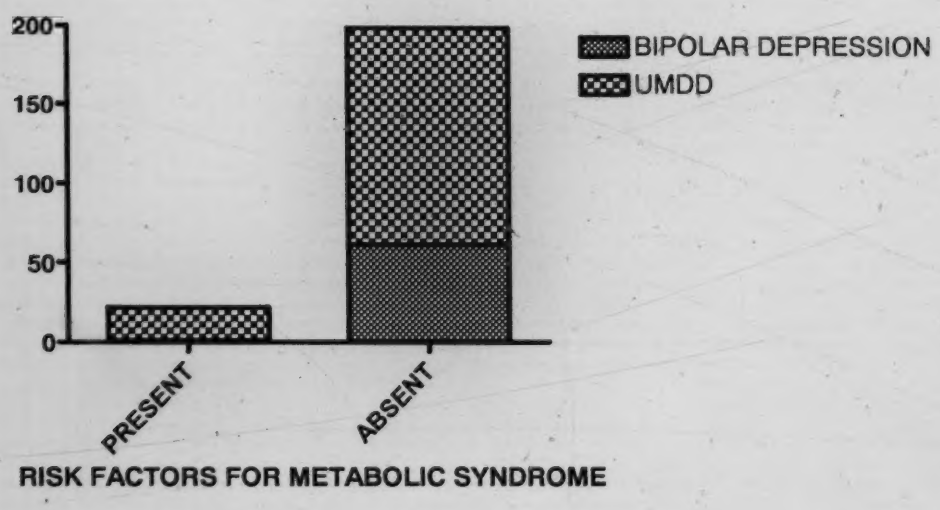
Alcohol use disorder was present in 15 of 187 (8.0%) of patients with UMDD, and 9 of 62 (14.5%) patients with bipolar depression. Any other substance use was present in 11 of 187 (5.9%) UMDD patients and 5 of 62 (8.1%) bipolar depressed patients. Mixed or polysubstance abuse disorder was present in 7 of 187 (3.7%) UMDD patients and 4 of 62 (6.5%) bipolar depressed patients. Taken together, a history of any substance use disorder was present in 18 bipolar depressed patients (29.1%) and 33 UMDD patients (17.6%) (Chi-squared 4.570, df: 1; P value=0.0325). This two-sided p-value was considered significant.

7.2.1.4 Pearson's exact test comparing bipolar depression and UMDD in regards to comorbid personality disorder.



Among the UMDD depressed patients a diagnosis of any comorbid personality diagnosis was made in 6 of 187 patients (3.2%) where the frequency was 9 of 62 (14.5%) in patients with bipolar depression. This increased comorbidity of personality disorder in bipolar patients was considered very significant (p=0.0031). Due to the small numbers, the chi-square test was not performed, as it would render a difficult to interpret value. The two-sided p-value of 0.0031 was obtained by analyzing data with the Pearson's exact test.

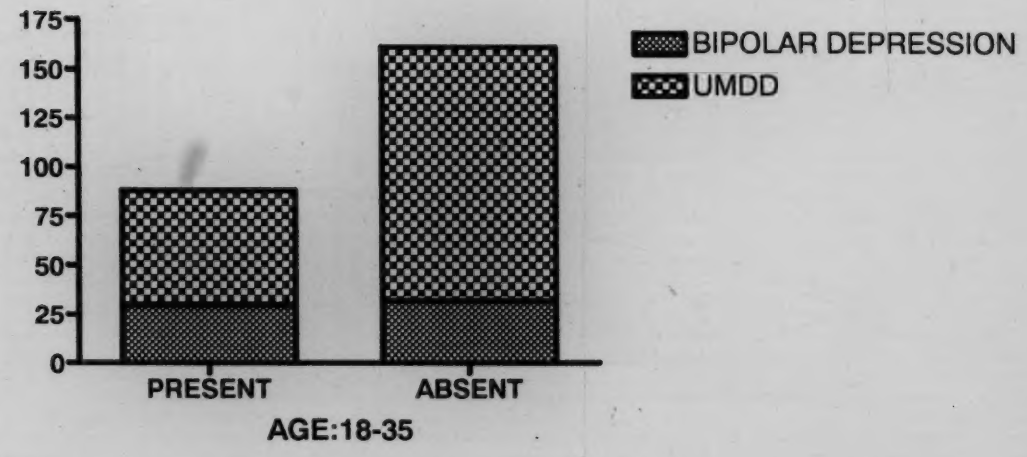
7.2.1.5 Pearson's exact test comparing bipolar depression and UMDD in regards to risk factors for metabolic syndrome.



Risk factors for metabolic syndrome was present in 21 of 187 (11.2%) UMDD patients, and only in 1 of 62 bipolar depressed patients (1.6%). This difference was considered very significant (Chi-squared 6.747, degree of freedom: 1, two-sided p=0.0094), suggesting that UMDD patients were at significantly higher risk of developing a metabolic syndrome compared to bipolar depressed patients.

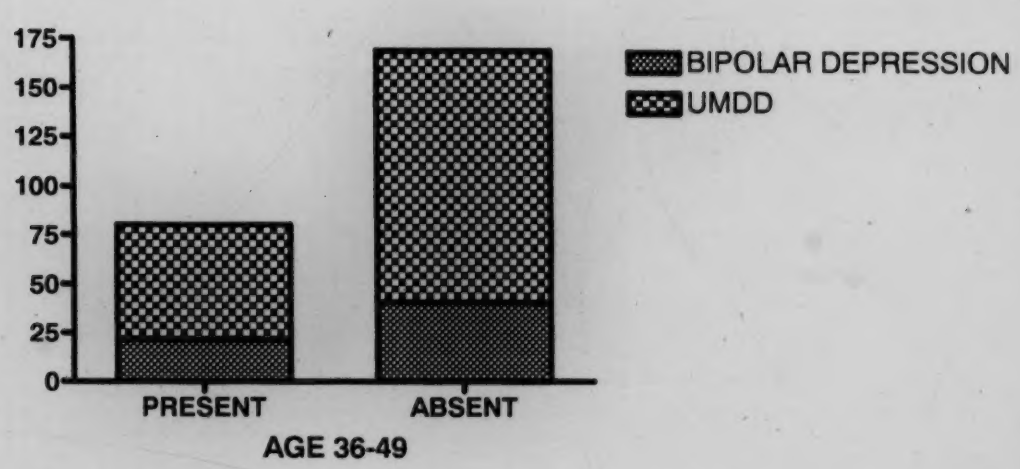
7.2.2 OTHER MEASUREMENTS:

7.2.2.1 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age groups 18-35.



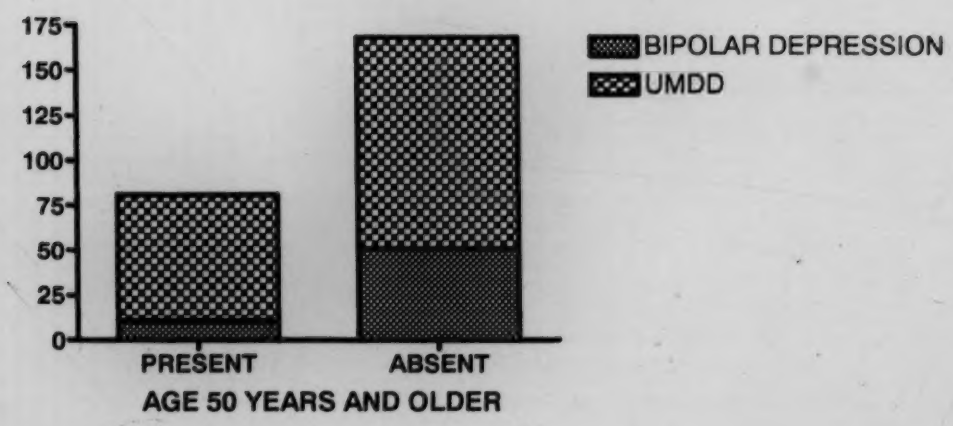
There was a significant difference among patients in our group who presented in the 18 – 35 age groups, with more bipolar patients being in this age group. Thus, among bipolar depressed patients, 30 patients (48.4%) were 18-35 years old while in comparison, among UMDD patients, 21 of 187 patients (11.2%) were in the age group 18-35. The two-sided p-value of 0.0148 was considered significant, suggesting that bipolar depression was present more often in a younger age-group than UMDD. However a p-value of >0.05 was considered not significant; the chi-square test could not be performed as the chi-square p-value would not be accurate.

7.2.2.2 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age group 36-49.



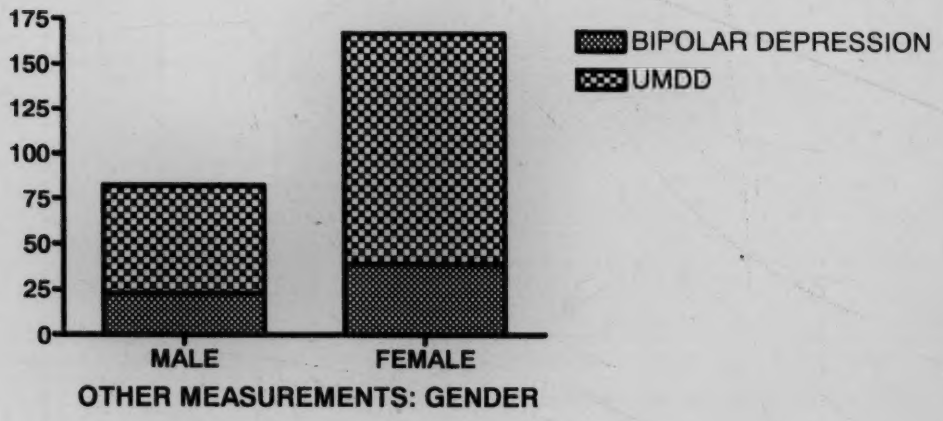
Among the bipolar depressed group, 21 patients (33.9%) were in the age group 36 to 49. Among the UMDD patients, there were 59 patients (31.6%) that were in the age group 36 to 49 years. The two-sided p-value of 0.7551 was considered not significant.

7.2.2.3 Pearson's exact test comparing bipolar depression and UMDD in regards to those in the age group older than 50



Among the bipolar depressed group, 11 patients (17.7%) were older than 50 (there were none older than 65). In contrast, among the UMDD patients, 70 patients (37.4%) were older than 50, including 7 patients older than 65. The two-sided p-value of 0.0046 was considered very significant, suggesting that more patients with UMDD than bipolar depression were older than 50. However, the chi-square p-value with these numbers would not be accurate and was not performed.

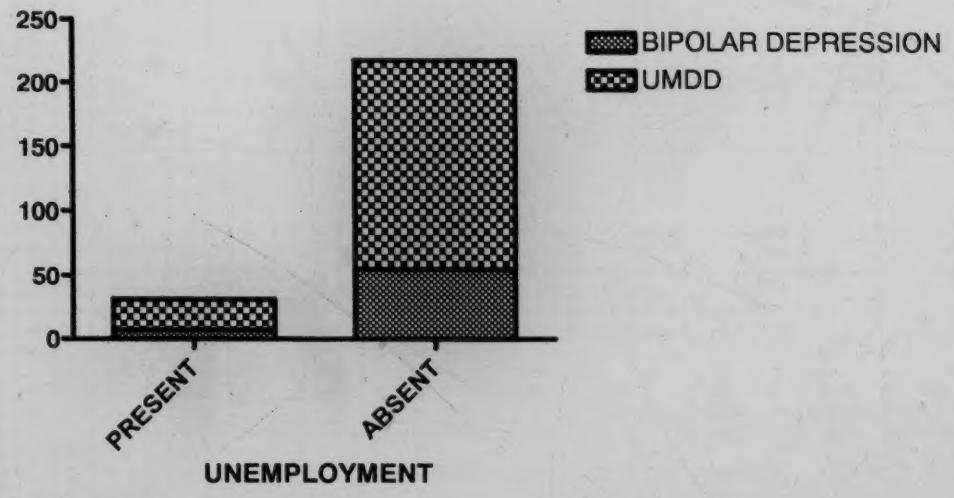
7.2.2.4 Pearson's exact test comparing bipolar depression and UMDD in regards to gender.



Among the 62 bipolar depressed patients, 23 patients (37.1%) were male and 39 patients (62.9%) were female. Similarly, among the 187 UMDD patients, 59 patients (31.6%) were male and 128 patients (68.4%) were female.

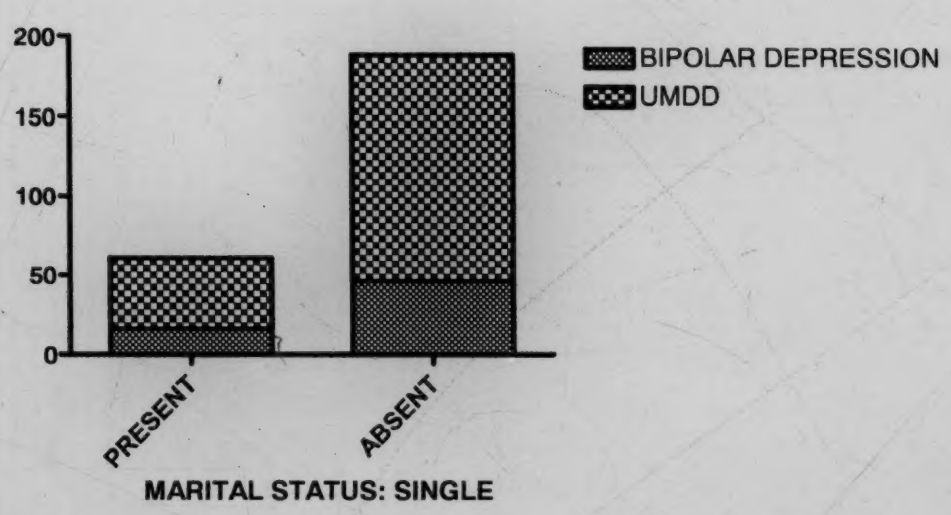
(Chi-square, df: 0.6484,1. Two-sided p value =0.4207). The chi-square p-value was not considered significant. Therefore there was no difference between the two groups in regards to gender.

7.2.2.5 Pearson's exact test comparing bipolar depression and UMDD in regards to unemployment.



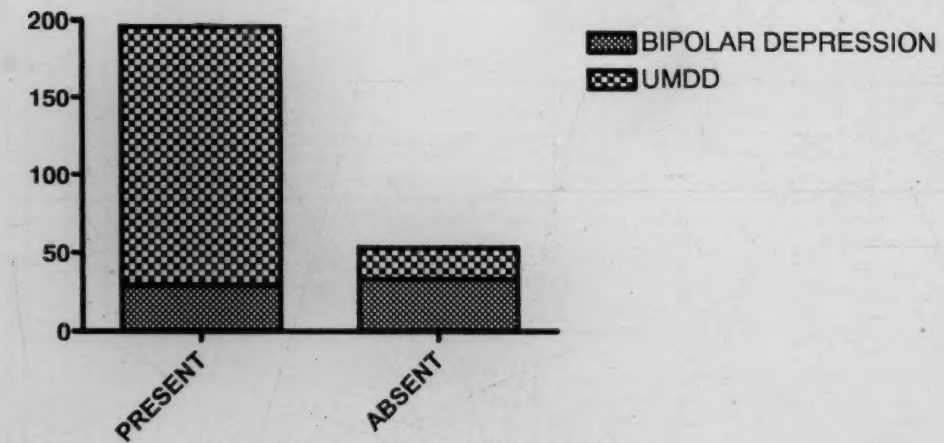
Among our bipolar depressed group, 55 of 62 patients (88.7%) were employed, including one patient who was retired, and two students. Unemployment was present among 7 patients (11.3%). Regarding UMDD patients, 158 patients (84.5%) were employed, including 5 patients who were retired and 5 students. Unemployment was present among 29 patients (15.5%). The two-sided p-value of 0.8280 was not considered significant. Therefore there was no meaningful difference between the two groups in regards to unemployment.

7.2.2.6 Pearson's exact test comparing bipolar depression and UMDD in regards to single patients.



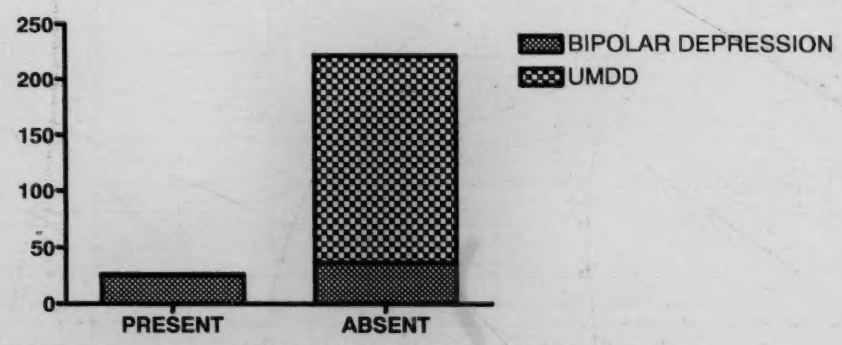
Of our bipolar depressed group, 16 patients (25.8%) were single or never married; 42 patients (67.7%) were married, and 4 of 62 patients (6.5%) were separated or divorced. In the UMDD group, 45 patients (24.0%) were single or never married, 131 patients (70.1%) were married, and 11 patients (5.9%) were either separated or divorced. The two-sided p-value of 0.8648 was not considered significant. Therefore there was no meaningful difference between the two groups in regards to being single.

7.2.2.7 Pearson exact test comparing bipolar depression and UMDD in regards to depressed mood as reason for referral.



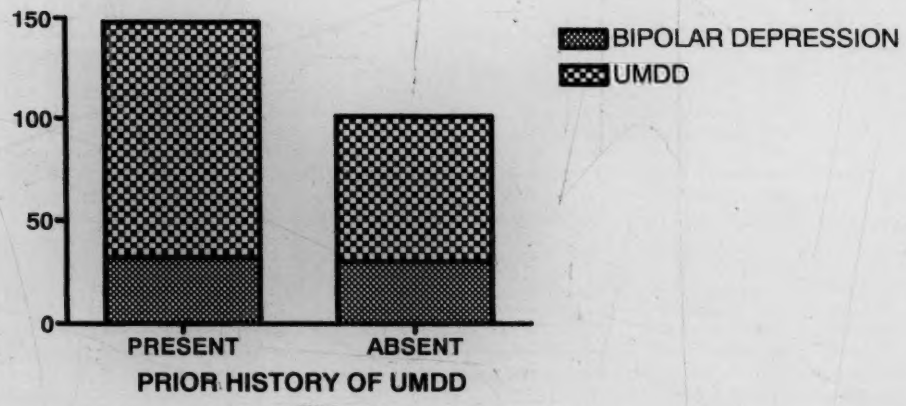
Of our patients with bipolar depression, 29 patients (46,8%) were referred for evaluation for depressed mood. Of the UMDD group, 167 of 187 patients (89.3%) were referred because of a depressed mood. P value<0.001. This two-sided p-value was considered extremely significant and more patients with UMDD than patients with bipolar depression were referred for evaluation of depressed mood. The chi-square p-value was not obtained, which would not have been accurate given the low numbers.

7.2.2.8 Pearson exact test comparing bipolar depression and UMDD in regards to "mood swings of unknown origin" as reason for referral.



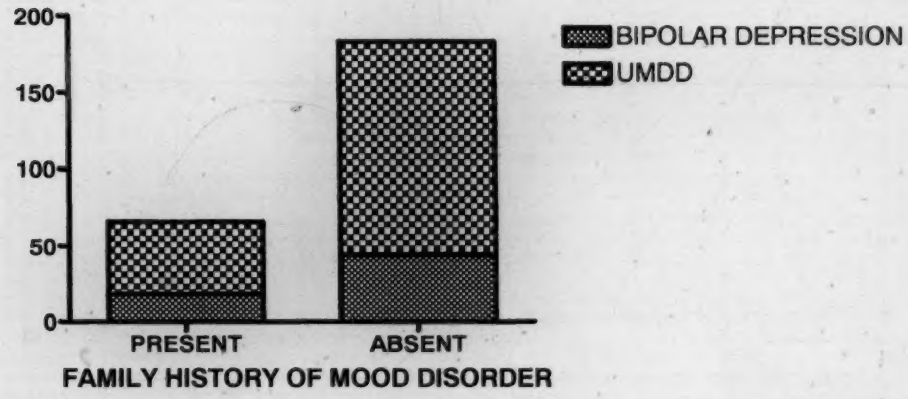
25 patients (40.3%) with bipolar depression were referred for evaluation of mood swings of unknown origin. Among the UMDD group, 2 patients (1.1%) were referred for evaluation of mood swings of unknown origin. The two-sided p-value was <0.001 and considered extremely significant, suggesting that more patients with bipolar depression were referred for "mood swings of unknown origin" than those with UMDD. The chi-square p-value would not be considered accurate with these small numbers and was therefore not obtained.

7.2.2.9 Pearson's exact test comparing bipolar depression and UMDD in regards to a prior history of UMDD.



Among the 62 bipolar depressed patients, 32 patients (51.6%) had a prior history of UMDD versus 116 patients (62%) of the UMDD patients with such a history. P value= 0.1792. This two-sided p-value was not considered significant, and therefore there was no meaningful difference between the two groups in regards to a prior history of UMDD.

7.2.2.10 Pearson's exact test comparing bipolar depression and UMDD in regards to a family history of mood disorder.



A family history of any mood disorder was present in 18 patients (29.0%) of the bipolar depressed group and 48 patients (25.7%) of the UMDD patients. The two-sided p-value was 0.6205, and therefore not considered significant.

8 DISCUSSION OF RESULTS.

8.1 COMORBIDITIES

In the study by McElroy and colleagues (2001) it was found that 65% of all patients with bipolar disorder experienced 1 or more lifetime comorbidities; 42% experienced 2 or more comorbidities, and 24% experienced 3 or more comorbidities. Vieta and colleagues (2000 and 2001) found comorbidities in 31% of patients with bipolar disorder. Using data from the Jorvi bipolar study, Mantere and colleagues (2006) showed that patients with bipolar disorder had a lifetime prevalence rate of 50.8% for a comorbid diagnosis. As noted below, our results differ somewhat from these previous findings.

8.1.1 ANXIETY DISORDER

Anxiety disorders occur frequently as comorbid conditions in UMDD and bipolar depression. According to a US comorbidity survey (Kessler et al., 1996), 58% of patients with UMDD have a comorbid anxiety disorder. In the study by Mantere and colleagues (2006), anxiety disorders were comorbidly present in 56.5% of 269 UMDD inpatients and outpatients. In contrast, anxiety disorders occurred in 44.5% of 191 inpatients or outpatients with a diagnosis of bipolar I or II disorders (Mantere et al., 2006). In the same study Mantere and colleagues (2006) could find no meaningful differences between bipolar I and bipolar II disorder in regards to comorbidities. According to other authors (McElroy et al., 2001; Simon et al., 2004) comorbid rates between 16% and 50% for anxiety disorders have

been found in patients with bipolar disorder. In another study, lifetime comorbidity of bipolar disorders with anxiety disorders was 75% (Merikangas et al., 2007).

In comparison, in our study comorbid anxiety disorder occurred significantly more frequently in patients with UMDD (38.5%) than in patients with bipolar depression (16.1%) (Chi-squared 17.4, $p < 0.001$). Interestingly, while the rate for anxiety disorders in patients with UMDD in our study was lower than in other reports, the rate of comorbid anxiety disorders was 16.1% among the bipolar depressed group, which was very similar to the McElroy study (2001), although certainly lower than other reported rates of 50% (Simon et al., 2004). The lower rates found in our study could be a reflection of the study population where only outpatients who were not severely ill were studied, and only the one most important comorbidity was recorded.

8.1.2 SUBSTANCE USE DISORDER

Regarding substance abuse, STEP-BD data (Simon et al., 2004) showed it to be comorbid in 37% of patients. Other studies have found a wide range of rates between 17% and 64% (Baldassano.2006). In the study by Mantere and colleagues (2006) 19.9% of patients with bipolar disorder had a current comorbid diagnosis for substance use disorders. Lifetime rates for alcohol abuse and dependence have been found to be 46.2% in bipolar I disorder patients, and 39.2%

in bipolar II disorder patients. In contrast, among patients with UMDD, 16.5% had a comorbid diagnosis of alcohol abuse or dependence (Baldassano et al 2006).

In our study we collected data for substance use disorders in our patients as both a current comorbid diagnosis and as a secondary measure where we noted a prior history of substance use disorder. Among the UMDD group, 9 patients (4.8%) of 187) and 5 patients (8.1%) with bipolar depression had a current comorbid diagnosis of any substance use disorder (p value=0.3466, which was not statistically significant). These rates are significantly lower than the rate that others have found (Baldassano et al., 2006). This may in part be explained by our methodology where we only documented the one most important comorbid Axis I or II disorders. Alternatively, it may be that drug and alcohol comorbidities are not as common in our Canadian population than in the other populations studied.

However, when we examined other measures, specifically looking at a prior history of any substance use disorder, this was positive in 17.6% of UMDD patients, and 29.1% of our bipolar depressed group and the statistical comparison was statistically significant (chi-squared 4.570; p-value=0.0325). When considering these revised data, this rate in bipolar patients is still lower than in previous studies , which may reflect differences in patient populations or drug use between populations as mentioned previously. Nonetheless, it is more similar to

the results found by others in that substance comorbidities are more frequently associated with bipolar disorder than UMDD.

8.1.3 PERSONALITY DISORDER AS A COMORBID DIAGNOSIS

Differences between UMDD and bipolar depressed patients in regards to an Axis II personality disorder comorbid diagnosis have been examined previously. According to Mantere and colleagues (2006) there was a tendency to have more clusters A personality disorders among UMDD patients compared to bipolar disorder patients (19.0% versus 9.9%), as well as a greater frequency of cluster C personality disorders in UMDD patients compared to bipolar disorder patients (31.6% versus 23%). In contrast, the same authors found more cluster B personality disorders, specifically borderline personality disorder, among patients with bipolar disorder compared to UMDD (30.9% of bipolar depressed patients versus 24.6% of UMDD patients).

In our study, while we did not differentiate among different personality disorders, there was a current comorbid diagnosis of personality disorder in 14.5% of the bipolar depression group and in only 3.2% of the UMDD group, a statistically significant difference between the 2 groups ($p=0.0031$). However, the prevalence of comorbid personality disorders overall are much lower than the Mantere findings. One explanation may be greater interviewer caution in making a comorbid diagnosis of a personality disorder in the presence of an axis I mood

disorder diagnosis, as well as our recording procedures where only the most important comorbid diagnosis was noted. It may also reflect differences in patient populations.

8.1.4 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

According to the STEP-BD data mentioned previously, Nierenberg and colleagues (2005) found that 9.5% of patients with a diagnosis of bipolar disorder had a lifetime diagnosis of ADHD. According to their study, ADHD predicted an earlier onset of bipolar disorder; with a tendency to be more present among males with a bipolar I disorder diagnosis. In stark contrast, among our entire mood disorder group, only 2 patients had a prior diagnosis of ADHD, and both these patients were male with a diagnosis of bipolar I disorder, depressed type (3% of the 62 bipolar depressed patients). We only had 4 patients with bipolar type I depression. Given this large discrepancy, it is of considerable interest to further study the possible association between bipolar disorder and ADHD. The best way to do this would be in a large prospective study of ADHD patients. A study, which followed up patients with ADHD for 6 years, found that nearly 30% of them switched to a bipolar diagnosis (Tillman et al., 2006). Given these high rates, it suggests that in our subject population there may have been a large underdiagnosis of ADHD in the past, possibly combined with poor recollection by patients of such a previous diagnosis.

8.1.5 MEDICAL COMORBIDITIES

Medical comorbidities have been reported to be frequent in patients with UMDD and bipolar depressed patients. We have looked at the presence of risk factors for metabolic syndrome in this thesis. According to a recent review article (Taylor et al., 2006) risk factors for metabolic syndrome, and therefore cardiovascular morbidity and mortality, have been associated with depression regardless of the use of medication. However, the use of atypical antipsychotic medication, which is frequently and effectively used in the management of serious mood disorders particularly bipolar disorder, has also been associated with a higher rate of metabolic syndrome (see chapter 3.6). Age also plays a role and it appears that the prevalence of metabolic syndrome as a medical comorbidity increases with age (McIntyre et al., 2007). In our study 21 patients (11.2%) with UMDD had risk factors for the metabolic syndrome, while it was only present in 1 patient with bipolar depression (1.5%). This difference was statistically significant (chi-squared: 6,747; p-value=0.0094). A possible explanation for this much lower presence among bipolar depressed patients could be their younger age in comparison to the older UMDD population, as well as the fact that only 21 patients (33.9%) had a prior diagnosis of bipolar disorder. The majority of bipolar patients (66.1%) had therefore not been treated with a treatment regimen likely to include atypical antipsychotics.

8.2 OTHER MEASURES.

8.2.1 AGE.

The relationship between mood and age has long been discussed, and it has been repeatedly shown that the mean age of onset for bipolar disorder is earlier than for UMDD (Allilaire et al., 2001; Shurhoff et al., 2002; Almeida et al., 2002; Merikangas et al., 2007). There is also the possibility that risk of depression can change with age. In this regard, it has been found that the interquartile range for age of onset of bipolar disorder was between the late teens and early forties, and there was a linear increase of lifetime prevalence in that age group (Merikangas et al., 2007). Looking at age differences in our population, there was a statistically significant difference (p=0.0148) among the age groups 18-35 and 50 and older (p-value was 0.0046). There was no statistical difference between bipolar depression and UMDD in the age group 36-49. The majority (82.3%) of our bipolar depressed population was under the age of 50, where this figure was 55 % for the UMDD group. In contrast, 17.7% of patients with bipolar depression versus 45% of the UMDD group were in the age group 50 and older. Therefore these findings show that patients who were subsequently diagnosed with bipolar depression were younger at the time they were referred to us, and this would support what others have found regarding the earlier age of onset of bipolar disorder compared to patients with UMDD.

8.2.2 GENDER

Regarding differences in gender prevalences, it has been known that in general UMDD and bipolar II disorder occur twice as often in women than men (DSM-IV). In contrast, a more recent lifetime and 12-month prevalence study (Merikangas et al., 2007) did find similar, but less marked, gender differences in patients with bipolar I disorder (male:0.8% versus female:1.1%) as well as bipolar II disorder (male:0.9% versus female:1.3%). We compared gender differences between our bipolar depressed group (consisting of 58 bipolar II depressed and 4 bipolar I depressed patients) and UMDD and found that both occurred twice as often in women than men. Our results, therefore, suggest that our bipolar depressed population are very similar to UMDD population in terms of sex distribution.

8.2.3 EMPLOYMENT STATUS

It is well known that mood disorders are among the leading causes of functional impairment and disability. In fact, the World Health Organization's Global Burden of Disease study ranked UMDD as the second highest cause of years lost to disability and premature death in the developing world. Bipolar disorder has been ranked sixth in this study (Simon et al., 2007). Depressive symptom severity among patients with bipolar disorder are important, as it was found in a recent study that even modest changes in the severity of depression had a statistically

and clinically significant effect on functional impairment and disability (Simon et al., 2007). It was interesting to note that in their study hypomanic or manic symptoms were less likely to be associated with functional impairment and disability. However it has been shown that the age of onset for bipolar disorder occurs earlier than UMDD and at a critical time for educational and occupational development (Merikangas et al., 2007; Angst, 2007). According to Angst (2007) the burden of bipolar disorder should be reassessed, as it is certainly underestimated.

In an earlier study (Peele et al., 2003) bipolar disorder was found to be the most expensive behavioral health diagnosis for patients and insurance plans in the United States. The total annual cost for bipolar disorder in the US has been estimated to be $45 billion (Kleinman et al., 2003). Indirect costs have been difficult to measure and included lost productivity due to absences from work, family and caregiver stress, and persons who committed suicide. In the study by Merikangas and colleagues (2007), patients with bipolar disorder were found to be ill for a decade of their lives.

Therefore it is important to look at employment status of patients with a depressive mood disorder. We found that 15.5% of UMDD patients and 11.3 % of bipolar depressed patients were unemployed, which were higher than predicted, and possibly indicative of the impact of affective mood disorders for this measurement. Note that we did not include patients who were booked off duty due to their illnesses, as they were still employed. The two-sided p-value of

0.8280 was not considered significant and therefore there was no meaningful difference between the 2 depressed groups for this measurement.

8.2.4 MARITAL STATUS: SINGLE OR NEVER MARRIED

Marital status is an important factor in illness progression, as it has long been recognized that prognoses for patients with mood disorders are more favorable if they are in a supportive interpersonal relationship (Kaplan and Sadock, 1997). Furthermore, bipolar disorder occurs more often in single and divorced people than among married people (Kaplan and Sadock, 1997). In our study, we found that 24.0% of UMDD patients and 25.8% of bipolar depressed patients were single or never married, but this difference was not statistically significant (p-value was 0.8648). Therefore no meaningful difference could be detected in the 2 groups in regards to single patients or patients that were not married before.

8.2.5 REASON FOR REFERRAL

Although "moodiness" and "mood swings" are vague terms and not often used in clinical research, the majority of our patients were referred for evaluation of "depressed mood" or "mood swings of uncertain origin". Benazzi and colleagues (2005) examined this trait in an outpatient setting among depressed patients with UMDD and bipolar II disorder who did not meet criteria for borderline personality disorder. They enquired whether a patient had frequent "ups and

downs" and whether these mood swings happened for no reason, and found that "mood swings" were present in 62% of patients with bipolar II disorder, and 37% of patients with UMDD (Benazzi et al., 2005). They made the conclusion that as a trait, mood lability had a relatively high (62%) sensitivity to diagnose patients with bipolar II disorder (Benazzi et al., 2005).

We were interested in assessing the reason for referral, as we believed it would reflect the underdiagnosis of bipolar disorder in our population. In this regard 29 patients (46.8%) that we diagnosed with bipolar depression were referred for depressed mood, where among the UMDD group, 167 patients (89.3%) were referred for depressed mood. 25 patients (40.3%) with bipolar depression were referred for "mood swings of uncertain origin" and 2 patients (1.1%) with UMDD were referred for this reason. The presence of "mood swings of unknown origin" in our population was lower than what Benazzi and colleagues found (2005). However it was definitely more present in our population of bipolar depression than among patients with UMDD. The two-sided p-value was <0.0001 that was considered highly significant. "Mood swings of unknown origin" might be a useful trait to use by general physicians; it may suggest that they may partially recognize the different clinical presentations more often than actual existing diagnoses suggest.

8.2.6 PRIOR PSYCHIATRIC HISTORY

We also documented prior psychiatric history. Among the bipolar depressed group 32 patients (51.6%) had a prior history of a UMDD diagnosis, and 21 patients (33.9%) had a prior history of bipolar disorder. Among the UMDD group, 116 patients (62%) had a prior history of UMDD.

Looking at reason for referral, prior psychiatric history, and our diagnostic findings, it can be argued that in our population of general physician referred patients, while UMDD was previously correctly diagnosed in the majority of depressed patients, the same cannot be said for bipolar disorder, which was certainly underdiagnosed, notwithstanding the partial recognition of "mood swings of unknown origin".

8.2.7 FAMILY HISTORY

In general, this is not always fully considered in clinical research, although it is well recognized that a family history of bipolar disorder should alert the clinician to this diagnostic possibility when a patient's index mood diagnosis is UMDD (Ghaemi et al., 2001). Where there is a history of recurrent UMDD in the family, it may even also imply the same course in the patient (Ghaemi et al., 2001). For these reasons it is important to obtain a family history of UMDD when assessing

patients. We compared the two groups in regards to a family history of mood disorder and could not find any meaningful difference between the two groups (the two-sided p-value was 0.6206, which was not considered significant.) However, a family history of any mood disorder was present in 29% of our bipolar depressed patients and 26% of patients with UMDD. Both groups reported a positive family history of mood disorders, given that we did not have collateral information on the majority of our patients.

9 PREVALENCE OF BIPOLAR SPECTRUM DISORDER IN 315 CONSECUTIVE OUTPATIENTS.

As discussed in our findings, bipolar (type I or II) depression is underdiagnosed, significantly associated with a range of comorbidities, and burdens the individual in all aspects of functioning. One of the reasons for the underdiagnosis of bipolar disorder is that the DSM-IV diagnostic criteria for this disorder are regarded by many as too restrictive. In this regard, it is argued that the broadening of criteria would be essential in capturing those with sub-threshold symptoms of bipolar disorder. Patients thus identified would then be included in the so-called bipolar spectrum disorder. The bipolar spectrum disorder as defined by Ghaemi and colleagues (2001) excludes bipolar type I and type II disorder, and encompasses those patients with sub-threshold criteria.

These sub-threshold criteria, or criteria suggestive of bipolar spectrum disorder, include: antidepressant–induced mania or hypomania; more than 3 recurrent major depressive episodes; psychotic major depressive episodes; a family history of bipolar disorder in first-degree relatives; a history of anti-depressant induced hypomania or mania; atypical depressive symptoms according to DSM-IV criteria; hyperthymic personality prior to the onset of depression; early age of onset (before the age of 25); and a highly recurrent pattern of illness with brief episodes. These symptoms are also sometimes called the "soft signs" of bipolar

disorder (Akiskal et al., 2006). Furthermore, atypical symptoms of depression, including hypersomnia, hyperphagia, fatigue, and sensitivity to rejection, are also regarded by other authors as strong indicators of underlying bipolar disorder spectrum disorder (Berk et al., 2006; Akiskal et al., 2006, and Benazzi, 2005).

Other suggested features of an underlying bipolar disorder have also been postulated to include postpartum onset of depression (specifically with psychotic features), a seasonal pattern, severe premenstrual syndrome, a lack of response to 3 or more adequate antidepressant trials, and an abrupt onset and end to an episode (Ghaemi et al., 2001; Berk et al., 2006). One of the major issues in diagnosing bipolar disorder has been the prevalence of bipolar spectrum disorder, which is of great clinical importance in any psychiatric practice. For this reason we have been interested in examining its presence in our patient population.

9.1 METHODOLOGY OF SCREENINGS

Following our initial assessments we carried out a secondary analysis of our patients. We specifically looked at patients that did not meet DSM-IV diagnostic criteria for bipolar I or bipolar II depression, to include a "bipolar spectrum disorder" group. In this regard, we looked at depressive features that were less likely to occur in UMDD. We followed the clues of sub-threshold bipolar disorder according to Ghaemi and colleagues (2001, 2002, and 2004).

Keeping these in mind, we examined all patient data from their charts and delineated an additional group with a history of current depressive episodes and current or past hypomanic features. The duration of hypomania was less than 4 days (i.e. failing to meet diagnostic criteria for hypomania). As with our bipolar depressed group, we only included those with current depressive features, to ensure broad diagnostic similarities with the bipolar depressed group. In other outpatient clinics it was not always clear if patients who were currently euthymic were excluded. In this group, we included those we have already diagnosed with cyclothymic disorder, and bipolar disorder, not otherwise specified. We also noted the presence of the atypical specifier among our patients. Using these criteria we identified an additional 39 patients in this "bipolar spectrum" group.

We then compared the 62 bipolar depressed patients with the 39 bipolar spectrum patients in regards to all comorbidities and other measurements. Tabulated Data were entered into contingency tables and nonparametric Pearson's exact tests, with a confidence interval of 95% were performed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

9.2 RESULTS SHOWING NUMBERS IN EACH MAJOR DIAGNOSTIC GROUPING

Among our 315 patients we now had six diagnostic categories:

A. In this group unipolar major depressive disorder (UMDD) was the primary diagnosis in 158 patients (50.2%)

B. As with our previous group, a primary diagnosis of psychotic disorder was made in 12 patients (3.8%).

C. A primary diagnosis of anxiety disorder was made in 19 patients (6.0%).

D. The bipolar depressed category remained the same and was the primary diagnosis in 62 patients (19.7%).

E. A primary diagnosis of bipolar spectrum disorder was made in 39 patients (12.4%).

F. Another primary diagnosis was made in 25 patients (7.9%).

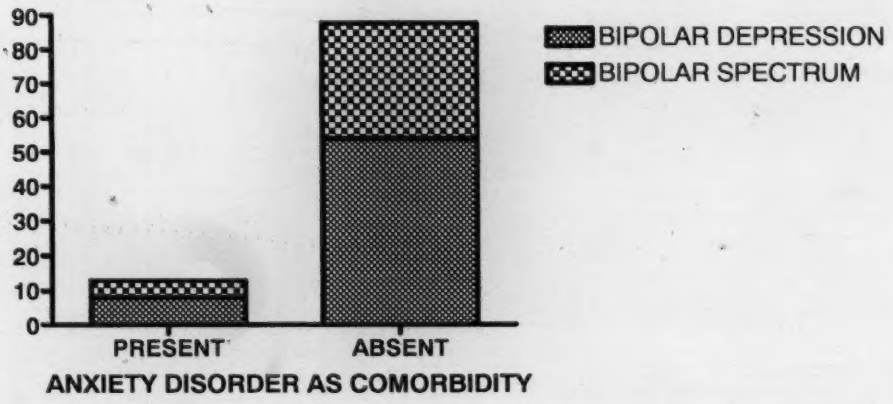
Of note is that the combined presence of bipolar depression and bipolar spectrum group was now 32.1% (n=101) of the total population in our revised grouping. We also noted the presence of the DSM-IV specifier, atypical depression. Among the UMDD group of 158 patients 9 females and 3 males (7.6%) had this diagnosis. Among the bipolar depressed group, 7 females, and 5 males (19.4%) fulfilled criteria for this diagnosis. Interestingly, among the bipolar spectrum group of 39 patients there was a much higher percentage of atypical features with 11 females and 1 male (30.8%) meeting criteria for this specifier.

We analyzed and compared the bipolar depression group with the bipolar spectrum group. We have hypothesized that the bipolar depressed group (only bipolar I and II depression) would not differ significantly from the bipolar spectrum disorder group in regards to comorbidities and other measurements.

9.3 RESULTS COMPARING 62 BIPOLAR DEPRESSED PATIENTS WITH 39 BIPOLAR SPECTRUM PATIENTS

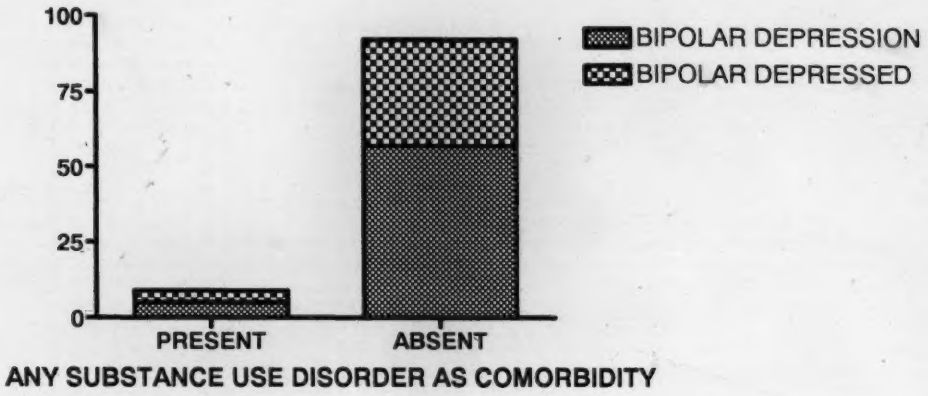
9.3.1 COMPARISON IN REGARDS TO COMORBIDITIES AMONG 62 BIPOLAR DEPRESSED PATIENTS AND 39 BIPOLAR SPECTRUM PATIENTS

9.3.1.1 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to anxiety disorder as comorbidity.



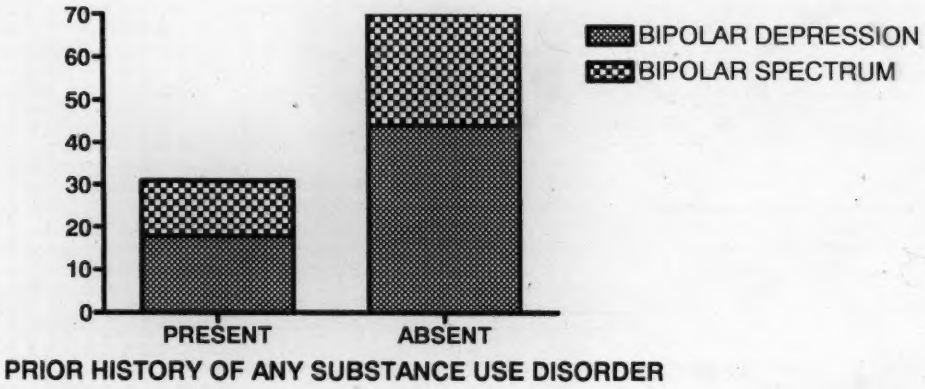
Among the 39 patients with bipolar spectrum disorder, 5 patients (12.9%) had a comorbid diagnosis of anxiety disorder, versus 8 patients (16.1%) of the 62 bipolar depressed patients. The two-sided p-value was 1.000, which was not considered significant. Therefore no meaningful difference was present between the two groups in regards to anxiety disorder as comorbidity.

9.3.1.2 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to any substance use comorbidity.



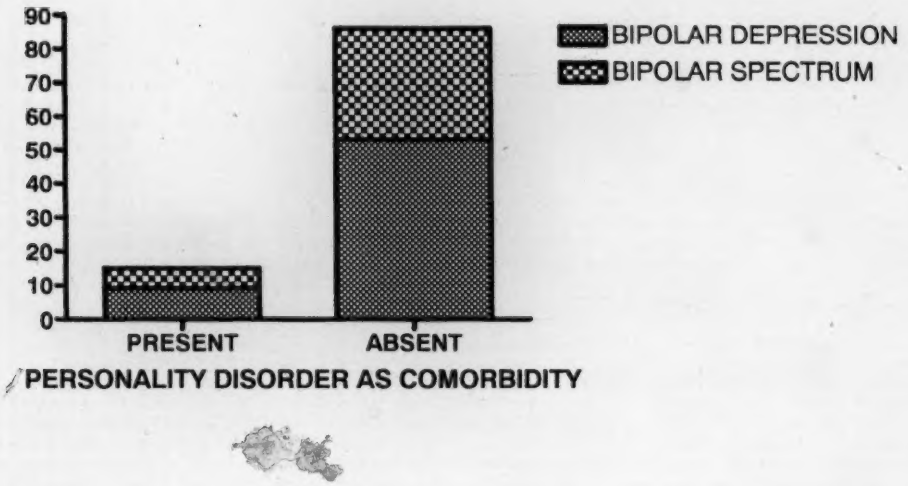
A comorbid diagnosis of alcohol and substance use disorder could be made in 4 patients (10.3%) of the bipolar spectrum patients and 5 patients (8.1%) of the bipolar depressed group. The two-sided p-value was 0.6638, which was not considered significant. There was therefore no meaningful difference between the two groups in regards to a comorbid axis I diagnosis of any substance use disorder.

9.3.1.3 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to a prior history of any substance use disorder.



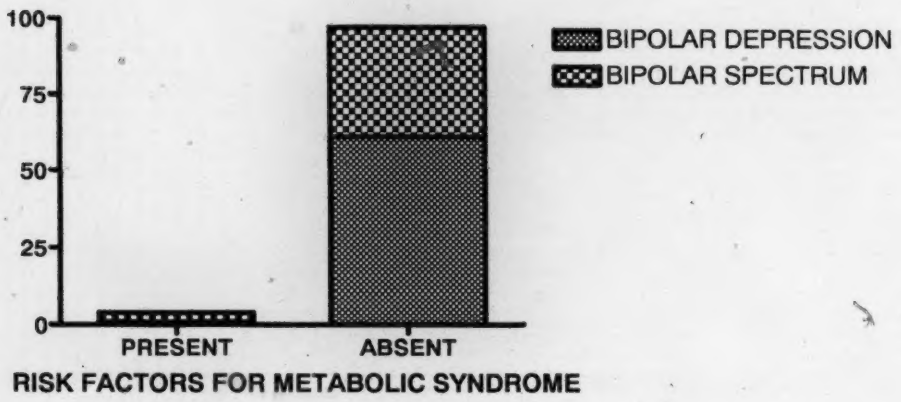
Looking at comorbid substance use disorder, we found alcohol use disorder in 3 patients (7,7%) of the bipolar spectrum group and 9 patients (14.5%) of the bipolar depressed group. Any substance use disorder, apart from alcohol use disorder was found in 4 patients (10.3%) of the bipolar spectrum group and 5 patients (8.1%)) of the bipolar depressed group. A diagnosis of mixed substance use disorder was made in 6 patients (15.4%) of the bipolar spectrum group and 4 patients (6.5%) in the bipolar depressed group. Taken together, 18 patients (29.1%) of patients with bipolar depression and 13 patients (33.4%) of patients with bipolar spectrum disorder had a prior history of any substance use disorder. The two-sided p-value was 0.7310, which was not considered significant and therefore no meaningful difference was present between the two groups in regards to a prior history of any substance use disorder.

9.3.1.4 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to personality disorder as comorbidity.



A personality disorder diagnosis was made in 6 of the bipolar spectrum patients (15.4%) and 9 patients (14.5%) of the bipolar depressed group. The two-sided p-value of 1.000 was not considered meaningful, and therefore no meaningful difference existed between the two groups in regards to a comorbid personality disorder.

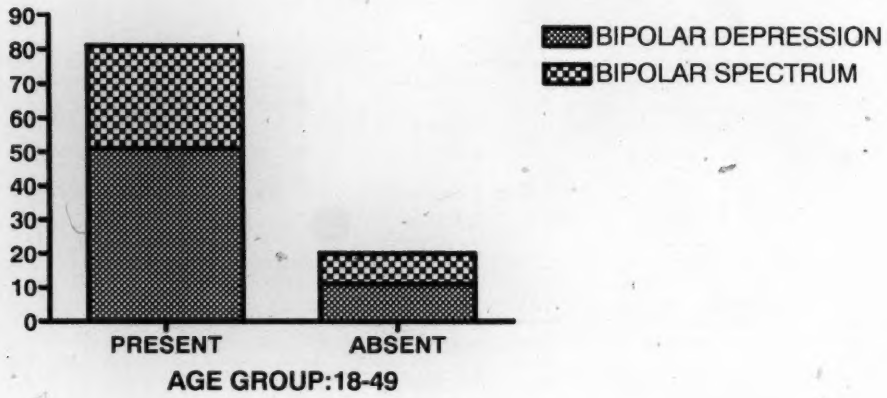
9.3.1.5 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to risk factors for metabolic syndrome.



Risk factors for metabolic syndrome could be diagnosed in 1 of the bipolar depressed group and 3 of the bipolar spectrum disorder. The two-sided p-value of 0.2956 was not considered meaningful, and there was therefore no meaningful difference between the two groups in regards to risk factors for the metabolic syndrome.

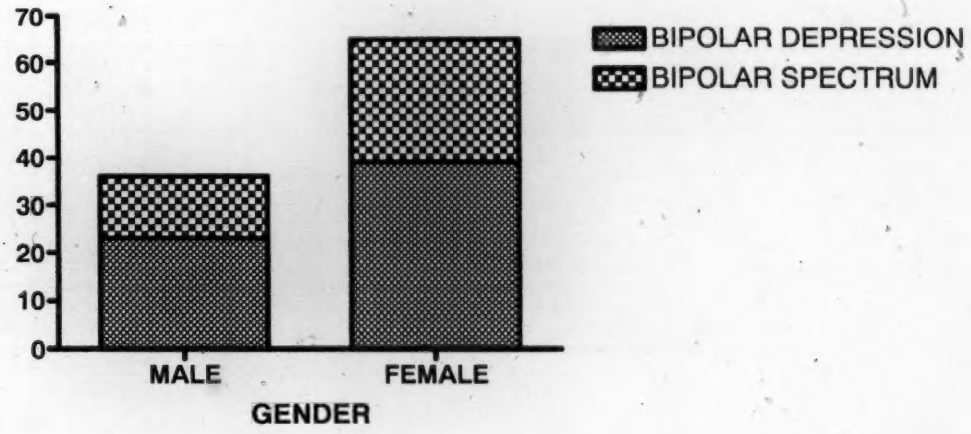
9.3.2 OTHER MEASUREMENTS

9.3.2.1 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to age group: 18-49.



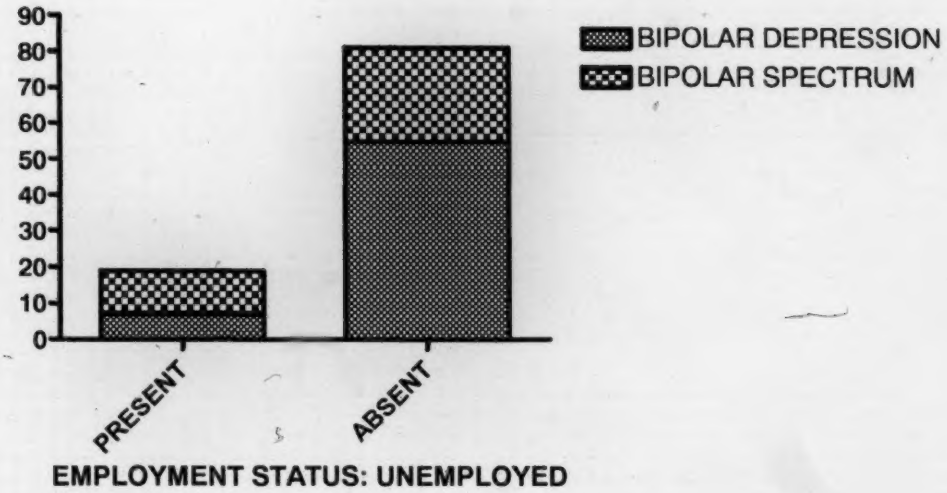
In regards to age group 18-49: 51 patients (82.3%) with bipolar depression were between the age of 18 and 49 versus 30 patients (77.0%) with bipolar spectrum disorder. The two-sided p-value of 0.6096 was not considered meaningful and therefore no meaningful difference was present between the two groups in regards to this age group.

9.3.2.2 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to gender.



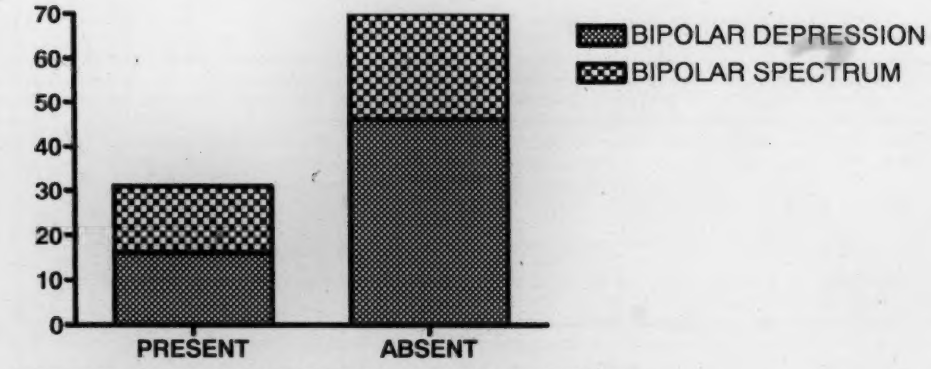
In regards to gender 13 patients (33.3%) of the bipolar spectrum group versus 23 (37.1%) of the bipolar depressed group were male; for females this figure was 26 (66.7%) in the bipolar spectrum group and 39 (62.9%) in the bipolar depressed group. The p-value was 0.8315 and therefore not considered significant. Therefore no meaningful difference was present between the two groups in regards to gender.

9.3.2.3 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to being unemployed.



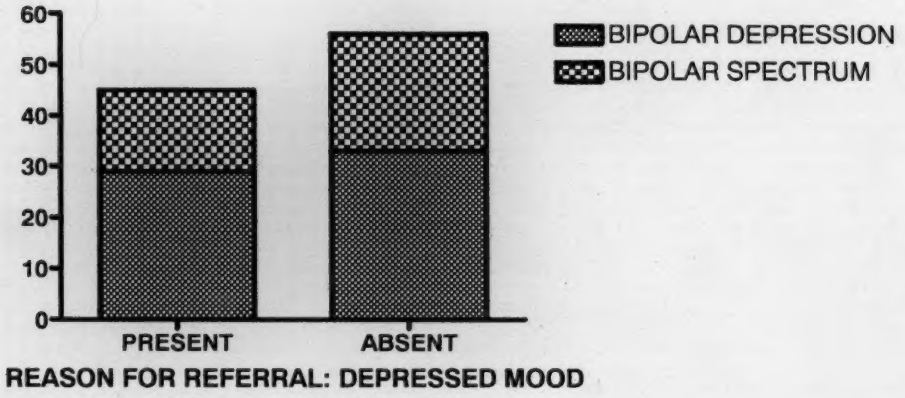
Of the bipolar spectrum group, 12 patients (30.8%) of the bipolar spectrum group versus 7 patients (11.3%) of the bipolar depressed group were unemployed. 23 patients (59.0%) were employed versus 52 patients (83.9%) of the bipolar depressed group. One patient in each group was retired. There were 3 students among the bipolar spectrum group and 2 among the bipolar depressed group. The two-sided p-value of 0.0176 was considered significant. Therefore a meaningful difference for unemployment existed between the two groups with more patients being unemployed among the bipolar spectrum group.

9.3.2.4 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum patients in regards to being single or never married.



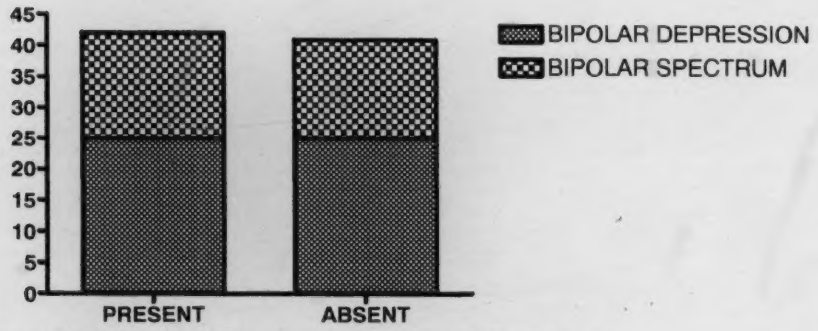
Among the bipolar depressed group 16 patients (25.8%) were never married or single whereas 15 patients (38.5%) of the bipolar spectrum group were single or never married. Of the bipolar depressed group, 42 patients (67.7%) patients were married versus 23 patients (59.0%) of the bipolar spectrum group. Four patients in the bipolar depressed group and one patient in the bipolar spectrum group were separated or divorced. We compared the two groups statistically in regards to being single. The two-sided p-value was 0.1919 and therefore not considered statistically significant. There was no meaningful difference between the two groups in regards to being single or never married.

9.3.2.5 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to depressed moods as reason for referral.



29 patients (46.7%) with bipolar depression and 16 patients (41%) with bipolar spectrum were referred for evaluation of depressed mood. The two-sided p-value was 0.6817, which was not considered significant. Therefore there was no meaningful difference between the two groups regarding this measurement. However in both groups the presence of bipolar illness was frequently missed.

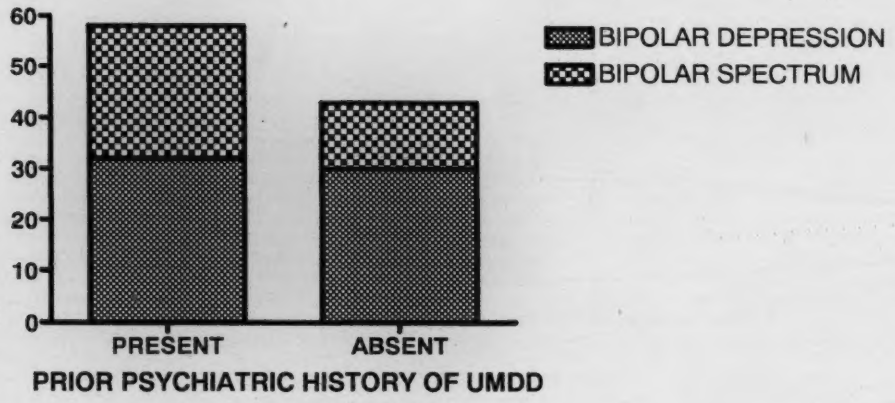
9.3.2.6 Pearson's exact test comparing 62 bipolar depressed patients and 39 bipolar spectrum disorder patients in regards to "mood swings of unknown origin" as reason for referral.



REASON FOR REFERRAL: MOOD SWINGS OF UNKNOWN ORIGIN

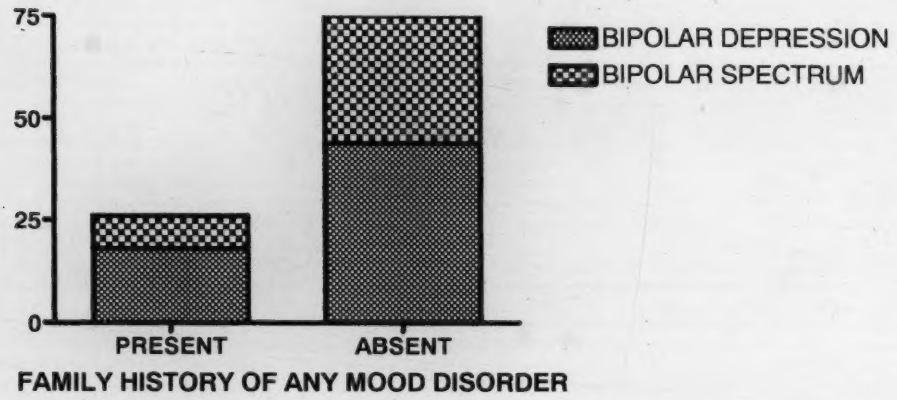
25 patients with bipolar depression (40.3%) and 17 patients (43.6%) with bipolar spectrum were referred for evaluation of mood swings of unknown origin. The two-sided p-value was 1.000, which was not considered significant. However mood swings of unknown origin were present in 40% of patients who were diagnosed with bipolar depression and 43% of patients who were diagnosed with bipolar spectrum disorder.

9.3.2.7 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to a prior psychiatric history of UMDD.



A prior history of UMDD was present in 32 patients (51.6%) with bipolar depression and 26 patients (66.7%) with bipolar spectrum disorder. The two-sided p-value of 0.1531 was not considered significant. However more than half of patients in each group had a prior history of UMDD.

9.3.2.8 Pearson's exact test comparing 62 bipolar depressed patients with 39 bipolar spectrum patients in regards to a family history of mood disorders.



A family history of mood disorder was present in 8 patients (20.5%) of the bipolar spectrum group and in 18 (29.0%) of the bipolar depressed group. The two-sided p-value was 0.4836, which was not considered significant, and therefore there was no meaningful difference between the two groups for this measurement.

10 DISCUSSION OF COMPARISON BETWEEN BIPOLAR DEPRESSED GROUP AND BIPOLAR SPECTRUM

10.1 SUMMARY OF STATISTICAL FINDINGS

It is interesting, that despite the claimed significant number of patients who belong the bipolar spectrum group, they have been relatively little studied. In terms of previous work comparing and contrasting them to bipolar depressed patients there is very little previous work, other than an article by Merikangas (2007) and some statements by Ghaemi and colleagues (2001).

10.1.1 COMORBIDITIES

10.1.1.1 Comorbid major diagnoses.

In our sample, we did not find differences in the comorbid presence of anxiety disorders, alcohol and substance disorders, personality disorders, and risk factors for metabolic syndrome. However, it should again be noted that we only included what we considered to be the single most important comorbid diagnosis. In a recent lifetime prevalence study, any anxiety disorder was found in 86% of patients with bipolar I disorder, 89% of patients with bipolar II disorder, and 63% of patients with sub-threshold bipolar disorder (Merikangas et al., 2007). We documented the current presence of anxiety disorder, which was present in 16% patients with bipolar depression, and 12% of patients with bipolar spectrum disorder. These differences are very large, and while in part may be explained by

a focus only on the single main comorbid diagnosis, other factors are likely to be present. One of these are likely to be the very different nature of the studies, where ours was a cross-sectional study in a much smaller population (315 patients) in comparison to the lifetime prevalence study by Merikangas and colleagues (2007), where 9282 patients were studied.

In the same study by Merikangas and colleagues (2007) any substance use disorder was found in 60% of patients with bipolar I disorder, 40% of patients with bipolar II disorder, and 35% of patients with sub-threshold bipolar disorder. We examined the history of any substance disorder in our patient populations, and found that 29% of patients with bipolar depression (type I and II) and 33% of patients with bipolar spectrum disorder reported such a history. These rates are much more similar between the two studies.

In our study, the low rates of risk factors for the metabolic syndrome could possibly be explained by the younger age groups and the absence of the use of antipsychotic mood stabilizers in the majority of bipolar depressed group (66%) and all the bipolar spectrum patients.

10.1.2 OTHER MEASUREMENTS

10.1.2.1 Age.

The mean age of onset for bipolar disorder is earlier than for UMDD (Allilaire et al., 2001; Benazzi, 2003). According to Ghaemi and colleagues (2001) the onset

of a depressive mood episode in patients younger than 25 should alert the clinician to rule out bipolar disorder. Among the different bipolar groups, namely bipolar I disorder, bipolar II disorder, as well as sub-threshold bipolar disorder, mean age of onset differences were found in a recent study (Merikangas et al., 2007) with an earlier onset in bipolar I disorder; bipolar II disorder had an earlier mean age of onset than sub-threshold bipolar disorder. The mean range of onset for all three disorders was between the late teens and early forties with a linear increase in lifetime prevalence in that age range (Merikangas et al., 2007). In our study, although we did not study the age of onset in our study populations, we noted that the majority of our patients (82% of bipolar depressed patients, and 77% of depressed patients with bipolar spectrum disorder) were under the age of 50. There was no meaningful difference between the two groups.

10.1.2.2 Gender

In general, bipolar I disorder occurs equally among men and women, where the ratio for men to women has been twice as often found in women than in men in bipolar II disorder (DSM-1V). Gender-specific differences (male and female) have also been reported for sub-threshold bipolar disorder and were present in 2.6% men and 2.1% women (Merikangas et al., 2007). However, in our study bipolar depression and bipolar spectrum disorder occurred among twice as many women than men.

10.1.2.3 Employment status.

As previously mentioned, bipolar disorders occur at a critical age for educational and occupational development (Angst, 2007; Merikangas et al., 2007). The risk for bipolar disorder has been found to be greater among the unemployed than the employed (Merikangas et al., 2007). In our study, we found that unemployment more than doubled among the bipolar spectrum disorder group (30.8%) in comparison with the bipolar depressed group (11.3%). Thus, though the symptoms of bipolar spectrum disorder may not be have reached current threshold diagnostic criteria, they could interfere with work functioning in a significant manner.

10.1.2.4 Marital status: single or never married.

In our statistical comparison of patients with bipolar depression and UMDD, no meaningful difference could be found, although a substantial number in each group (24% in UMDD and 25% in bipolar depression) never married or were single. In the bipolar spectrum disorder group, 38% of patients were single or never married. This difference was not considered meaningful. Sub-threshold bipolar disorder (but not bipolar type I or II disorder) was found to be elevated in patients who were previously married (Merikangas et al., 2007). We did not found this difference in our study.

10.1.2.5 Reason for referral and prior psychiatric history.

We were interested in assessing the reason for referral, because we believed it would reflect the underdiagnosis of bipolar disorder. We compared the two groups and could not find any meaningful differences. Roughly 40% of patients in each group were referred for evaluation of either depressed mood or mood swings of unknown origin. Only 21 patients (34%) of the bipolar depression group was prior diagnosed. More than 50% in each of our groups were previously diagnosed with UMDD.

10.1.2.6 Family history of psychiatric illness.

According to Ghaemi and colleagues (2001) a family history of bipolar disorder is an important clue for bipolar spectrum diagnosis. In the study by Kiejna and colleagues (2005) a family history of bipolar disorder increased the likelihood of both bipolar II disorder and bipolar spectrum disorder. A flaw in this thesis is that we did not have collateral information in the majority of patients. Although we did not collect information for a family history of bipolar disorder mood disorder, we did note that a family history of any mood disorder was present in 29.0% of the bipolar depressed group and 20.5% of the bipolar spectrum group.

10.2 Frequency

As noted by Akiskal and colleagues, when they used modified diagnostic criteria for hypomania using only 2 or more days of hypomania, they found that such a

modified form of bipolar II disorder occurred in 56.8% of consecutive outpatients who until that time only had a diagnosis of major depressive disorder (Akiskal et al., 2005). Further support for this hypothesis comes from Angst (2006) who suggested that 40% to 60% of patients in psychiatric practice with a diagnosis of major depressive disorder should have received a diagnosis of bipolar II disorder.

In contrast, looking at clues for bipolar disorder, as set out by Ghaemi and colleagues (2001), Kiejna and colleagues (2005) could identify a further 12.6% of their patients with a prior diagnosis of UMDD.

In our study, we also looked for bipolarity as suggested by Ghaemi and colleagues (2001, and 2004) among our entire patient population of 315. As noted, these authors have suggested that specific factors that could indicate a high likelihood of an underlying bipolar spectrum disorder include: a family history of bipolar disorder in first-degree relatives; a history of anti-depressant induced hypomania or mania; hyperthymic personality prior to the onset of depression; an early age of onset (before the age of 25); a highly recurrent pattern of illness with brief episodes, and atypical features of depression, including hypersomnia, hyperphagia, fatigue, and sensitivity to rejection. They have also indicated that the bipolar spectrum would include cyclothymic disorder, and bipolar disorder not otherwise specified to delineate the spectrum separate from bipolar I and II disorders.

Using similar tools we identified an additional 39 patients (12.4%) who belonged to the bipolar spectrum. This was a very similar finding to those of Kiejna and colleagues (2005). Interestingly, 2 patients had a prior diagnosis of substance induced hypomania; 3 patients had previously been diagnosed with cyclothymic disorder, and 5 patients were diagnosed as having bipolar disorder, not otherwise specified. Of the original 187 patients that were given a diagnosis of UMDD, we delineated 29 patients who belonged to the bipolar spectrum.

Additionally, we specifically looked at the presence of the DSM-IV atypical specifier and diagnosed this among 12 patients (30.8%) with bipolar spectrum disorder. The majority of patients (11 of 12) were women. Benazzi has found that atypical depression had twice the likelihood to occur among patients with bipolar II disorder than UMDD (Benazzi et al., 2000). Of our patients with bipolar depression, 12 patients (19.4%) had atypical depression. Among our UMDD group, 12 patients (7.6%) had a diagnosis of atypical depression, confirming what Benazzi found in his outpatient study.

Some authors have suggested that combining the hard bipolar I and II disorder with the soft bipolar spectrum disorders may account for 65% of major depressive episodes, making it more prevalent than major depressive disorder (Akiskal et al., 2006). However, in our study we could not confirm this. Thus, while the total numbers of patients with UMDD were 187 (59.4%) and 62 patients (19.7%) with bipolar depression, when the bipolar spectrum group was included the numbers

changed. There were 158 patients (50.2%) with UMDD and 101 patients (32.1%) in the combined bipolar group. Nonetheless, since only 21 patients (6.7%) in the referral population of 315 patients had been diagnosed with a bipolar depression prior to referral, the percentage of patients with bipolar depression is underestimated.

11 MEASUREMENT OF SEVERITY OF DEPRESSION

In addition to clinically assess mood in our patient population of 315 patients, in a small percentage of patients standardized measurements of depression were made, and these are reported here.

The first measure was the Hamilton Depression Scale (HAM-D, Hamilton 1960), although it has been argued that this can be unreliable as there may be many problems in regards to inter-rater reliability and also because it lacks explicit scoring procedures, (Tabuse et al., 2007). Nonetheless, the HAM-D is still extensively used in clinical research. Different versions of the HAM-D are in use, for example the HAM-D-17 (which we used), the HAM-D-31 and a recent short version, the HAM-D-7 (McIntyre et al., 2002).

Another scale, the Montgomery-Asberg-Depression Rating Scale (MADRS; Montgomery et al., 1979) has been shown to be an efficient and practical measurement of depression severity without the inter-rater reliability problems associated with the HAM-D.

Both the HAM-D and the MADRS have been extensively used in clinical research to measure outcome in anti-depressant efficacy trials. There has been some indication that the MADRS might be more accurate in estimating depression than the HAM-D. In a recent study by Carmody and colleagues (2006) among 233

highly resistant depressed outpatients, the authors concluded that the MADRS would be superior to the HAM-D-17 in clinical trials. In their study, the MADRS showed twice the precision to estimate depression than the HAM-D-17. Benazzi (1999) did a study among 405 outpatients using the MADRS to see whether there would be a difference between UMDD and bipolar II depressed patients. He could find no differences. However, when he compared differences between atypical bipolar II and non-atypical UMDD there was indeed a difference. There was a significant difference on two MADRS items, namely reduced sleep and reduced appetite. Reduced sleep (MADRS Item 4) measures the patient's reduction in duration or depth of sleep and is rated on a scale of 0 to 6, where 0 represents sleeping as normally, and 6 represents sleeping less than 2 or 3 hours. In regards to the MADRS Item 5, reduced appetite, a score of 0 indicates normal or increased appetite, and 6 indicates a complete loss of appetite, where the patient would not eat at all, unless being persuaded to do so. Looking at the reversed vegetative criteria for the atypical specifier, specifically hypersomnia and increase in appetite, it is clear that patients with or without atypical depression might have different scores, which could be misleading.

The HAM-D and MADRS have been successfully translated into different languages. A questionnaire that combined the MADRS and HAM-D31, was recently described that could improve consistency and validity of study findings (Iannuzzi et al., 2006).

In terms of scores on these scales, remission of depression has been defined as a score below a cutoff on severity measures. On the MADRS this would correspond to a score equal to or less than 4 (Zimmerman et al., 2004). On the HAM-D17, remission has been defined as a score < 8, and in a large study consisting of 2,027 subjects, two items, namely depressed mood (item 1) and psychic anxiety (item 10) were found to be useful in predicting remission (Silverstone et al., 2002). Moderate severity of depression would correspond to a cutoff point of 18 on the HAM-D17 and 20 on the MADRS, which was also the cutoff point used in studies at our clinic. According to Muller and colleagues (2000) a MADRS score of 35 and a HAM-D score of 28 should be the cutoff point for severe depression.

Taking all of this into account, we were interested to ascertain possible differences between the HAM-D17 and MADRS in some of our patients.

11.1 PATIENT POPULATION USED TO COMPARE HAMD-17 AND MADRS

In the present study we used the HAM-D17 and the MADRS in a subset of 41 patients to help quantify possible differences in depression measurements. Depression severity was measured in 27 patients with a diagnosis of UMDD and 12 patients with a diagnosis of bipolar depression. Both UMDD patients and bipolar depression patients were categorized into 3 groups according to severity of depression. We defined severity of depression as follows:

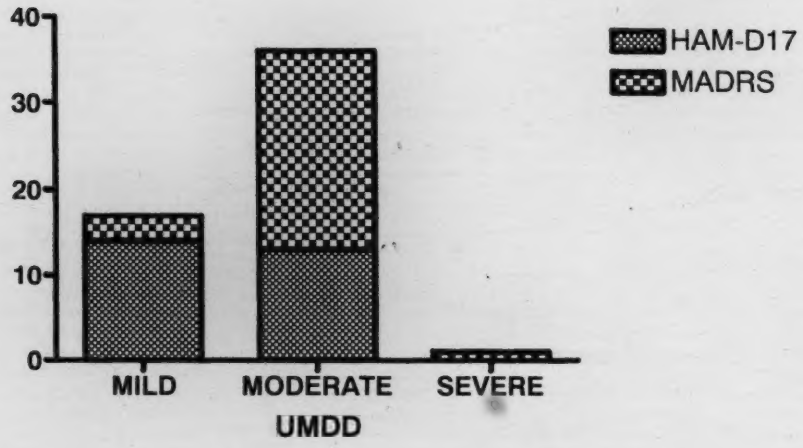
a. Mild depression was defined by a value of 10-17 on the HAM-D17 and 12-19 on the MADRS.

b. Moderate depression was defined as a value of 18-28 on the HAM-D17 and 20-35 on the MADRS.

c. Severe depression was defined as a value of >28 on the HAM-D17, and >35 on the MADRS.

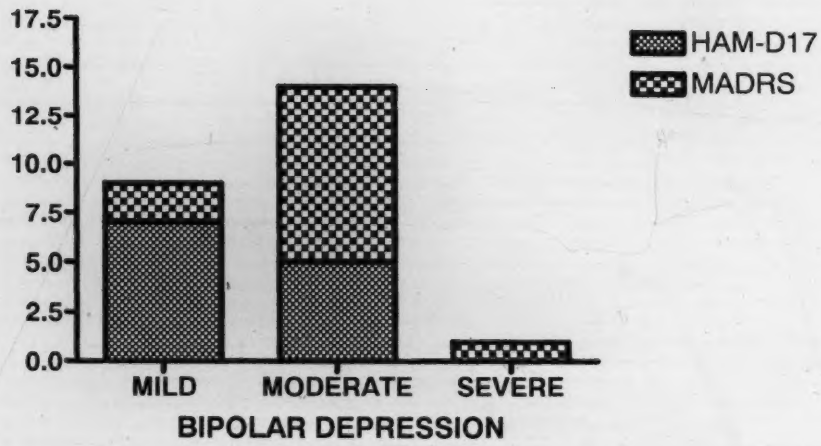
We used the same methods as described in chapter 7. Tabulated Data were entered into contingency tables and nonparametric Chi-square tests, with a confidence interval of 95% were performed using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com. Nonparametric tests were used. We firstly compared the HAM-D17 and MADRS in 27 patients with UMDD. Secondly, we compared the HAM-D17 and MADRS in 12 patients with bipolar depression.

11.1.1 CHI-SQUARE TEST COMPARING HAM-D17 AND MADRS AMONG PATIENTS WITH UMDD.



Using our definitions of severity for the HAM-D17, mild depression was present in 14 of the 27 patients, where moderate depression was present in 13 patients. There were no patients with severe depression. In contrast, using the MADRS, we could identify 3 patients with mild depression, 23 patients with moderate depression, and 1 patient with severe depression. The chi-square p-value was 0.0043, which was considered very significant (chi-square:10.90; degree of freedom :2), and shows that even in small groups such as this currently used rating scales can differ widely in their interpretation depending upon the cut-off points used.

11.1.2 CHI-SQUARE TEST COMPARING HAM-D17 AND MADRS AMONG PATIENTS WITH BIPOLAR DEPRESSION.



Using our definitions of severity of depression for the HAM-D17, mild depression was present in 7 patients, and 5 patients had moderate depression. There were no patients with severe depression. In contrast, using our criteria for depression for the MADRS, 2 patients had mild depression, 9 patients had moderate depression and 1 patient had severe depression. The chi-square p-value was 0.1737 (chi-square: 3.501; degree of freedom: 2), which was not considered significant.

11.2 DISCUSSION OF FINDINGS

As mentioned previously, some authors have claimed that the MADRS might be a more sensitive instrument in measuring depression severity than the HAM-D. Most authors however could not find such a difference. Among our patients with UMDD there was a difference, and the MADRS identified more patients with a moderate severity of depression than the HAM-D17. There was no meaningful difference in patients with bipolar depression using the HAM-D17 and MADRS.

The difference among the two measurement scales in patients with UMDD should be interpreted cautiously, as this data comes from only a small (possibly unrepresentative) subset of the subjects.

12 SUMMARY OF FINDINGS AND CONCLUSIONS FROM THESIS

12.1 Weaknesses of study design

There are several limitations in this study.

1. Single-interviewer bias could have been a problem, as there was no rigorous mechanism to ensure that the two interviewers always would have reached the same diagnostic conclusion. In terms of diagnostic exactitude, it would have been useful to obtain systematic collateral information on all patients.

2. In addition, screening tests could have been performed on all patients. The reason why all patients were not screened is because most patients were not included in other studies which did not form part of this study. In those studies patients were all screened using the HAM-D17 and the MADRS.

3. In terms of other factors, obtaining standardized and systematic information on all patients to compile a history of childhood psychiatric problems, including a history of ADHD, any anxiety and mood disorder symptoms, any prior psychiatric diagnoses, and treatment, specifically noting the age of onset of symptoms, might have allowed more accurate determinations than simply patient recollections. Similarly, a family history of psychiatric illness would also be more accurate when collateral information is obtained. A carefully obtained collateral history would also enable one to record a more accurate prior or current history of comorbidities, including psychiatric comorbidities. A history of medical

comorbidities, especially the presence of risk factors for metabolic syndrome would be essential, and in this regard, a complete medical history provided by family physicians might have been helpful.

4. This study was a single cross-sectional diagnosis of the patient's condition, and it is quite possible that different results would be obtained from large, well-controlled, longitudinal studies of this patient group.

12.2 Summary of findings.

Despite the limitations identified above, this study had a number of strengths. The first is that this was from a large group of consecutive patients who may have been more representative of patients seen by general psychiatrists than in other studies. Compared to much of the existing literature, this group was much larger than those often reported. Also, strict diagnostic criteria were used to study the prevalence of bipolar depression and bipolar spectrum disorder. Lastly, we considered multiple factors including comorbid conditions and atypical symptoms that frequently haven't been well delineated in this population.

Given this, our findings are as follows:

1. Studies suggest that when broad criteria for diagnosis are used, 40 to 60% of patients with a prior diagnosis of UMDD should in fact be diagnosed with bipolar disorder. In the present study, using strict DSM-IV criteria, bipolar depression was present in 19.7% of our population while UMDD was present among 59.4%

of our population. A further 12.4 % of our population was diagnosed with bipolar spectrum disorder, using criteria by Ghaemi and colleagues.

2. We found statistically significant differences between the two groups when we looked at comorbidities and other measurements:

2.1. Any anxiety disorder was present more among patients with UMDD than bipolar depression (38.5% versus 16.1%; two-sided p-value <0.001).

2.2. Any personality disorder was present more often among the bipolar depressed group than the UMDD group (14.5% versus 3.2%; two-sided p-value was 0.0031).

2.3. A prior history of substance abuse disorder was more often present in the bipolar depressed group than in the UMDD group (29.1% versus 17.6%; two-sided p-value was 0.0325).

2.4. Risk factors for the metabolic syndrome were more often present among the UMDD group than the bipolar depressed group (11.2% versus 1.6%; two-sided p-value was 0.0094).

2.5. The bipolar depressed group was significantly younger than the UMDD group in the age group 18-35 (two-sided p-value was 0.0148), where there were statistically significant more people among the UMDD group than the bipolar depression group older than 50 (two-sided p-value was 0.0046).

2.6. More patients who were referred for evaluation of "mood swings of unknown origin" were diagnosed with bipolar depression than UMDD (two-sided p-value<0.001).

3. We found few differences between the two groups in regards to other measurements:

3.1. Twice as many women than men had UMDD or bipolar depression.

3.2. Among the two groups marital status was similar, and we noted that 25.8% of the bipolar depressed group and 24.0% of the UMDD group were single or never married.

3.3. Employment status were similar between the two groups and we noted that 11.3% of the bipolar depressed group and 15.5% of the UMDD group were unemployed.

3.4. A prior psychiatric history of UMDD was present in both groups: 62% of patients with UMDD and 51.6% of patients with bipolar depression.

4. When we used diagnostic criteria described by Ghaemi and colleagues we could delineate an additional group of 39 patients (12.6%) where we could make a diagnosis of bipolar spectrum disorder. This is similar to what others have found, who used the same criteria.

We were also interested to see if any differences existed between the two groups in regards to comorbidities and other measurements, and found that apart from employment status there were no meaningful differences between the two groups. However, the bipolar spectrum disorder group was more likely to be unemployed than the bipolar depressed group.

5. We also looked at the presence of the atypical depression specifier and found this more frequently present among patients with bipolar spectrum disorder (12 of 39 patients) than among patients with bipolar depression (12 of 62 patients). There was a difference in gender for this measurement in that of the 12 patients in each group, there were 11 women in the bipolar spectrum disorder group and 7 women in the bipolar depressed group.

6. Finally, we briefly compared two measuring instruments, namely the HAM-D17 and the MADRS, in a small subset of our patients and found that in patients with UMDD, but not in patients with bipolar depression the MADRS identified more patients with moderate depression than the HAM-D17. We only used these two measuring instruments in 39 patients.

12.3 CONCLUSION.

We have found that bipolar disorder in depressed patients is often missed. In our outpatient clinic where we used strict criteria we could identify the presence of

bipolar depression in 19.6 % of our patients. Using criteria according to Ghaemi and colleagues, we could identify an additional 12.6% of patients to include in the bipolar spectrum disorder.

In our study there were significant differences between patients with bipolar depression and UMDD patients with a younger population among the bipolar depressed group, who had more substance use disorders and personality disorders as comorbidities. The UMDD patients were from an older population, who had more anxiety disorders and risk factors for metabolic syndrome as comorbidities. Both these groups had similar unemployment rates, which were higher than expected.

The only difference between the bipolar depression group and the bipolar spectrum disorder group was a significantly higher unemployment rate among the bipolar spectrum group. This might reflect how underdiagnosis can lead to functional impairment in this group.

Sufficient clinical skills are therefore essential to ensure appropriate pharmacological managements and better functional outcomes for those depressed patients who in fact have a bipolar illness.

12.4 FUTURE DIRECTIONS.

Comorbidities occurred frequently in our patient population with bipolar depression, although our figures are not as high as others have reported. We believe, however that a thorough clinical assessment is essential to uncover symptoms of bipolarity and comorbid conditions. It appears that bipolar depressed patients share similarities with bipolar spectrum patients in our populations. Clearly, this is an under-researched area.

Currently a significant group of patients with bipolar depression are excluded from treatment and imaging studies because of Axis I, II and III comorbidities. Additionally patients who do not reach DSM-IV threshold criteria for bipolar depression are excluded. Including these patients will be more reflective of clinical psychiatric practice populations.

Although not used in our study, screening tests for bipolar disorder and bipolar spectrum disorder are available. One such test is the "Mood Disorder Questionnaire" (MDQ) developed by Hirschfeld and colleagues (2000). This is a brief self-report screening instrument that is increasingly being advocated for use in clinical practice (Muzina, 2007). Another screening tool is the "Bipolar Spectrum Diagnostic Scale" (BSDS) developed by Ghaemi and colleagues (2005). This test is also a brief self-rating test that is easy to administer. It has

been suggested that the BSDS has strong correlations with other depression rating scales, including the MADRS and HAM-D (Berk et al., 2007).

Apart from the MDQ and the BSDS, the HAM-D17 and MADRS should be performed on all patients with the patients ideally being screened on the HAM-D and MADRS by a separate interviewer.

It might be an option in future studies to include bipolar depressed patients with comorbidities and subthreshold criteria as defined by Ghaemi and colleagues in future studies. Furthermore, it would be essential to obtain comprehensive collateral information on all future patients at the mood disorder clinic, apart from a thorough clinical psychiatric evaluation. The use of screening instruments should be used in all patients.

TABLE 1: COMPARING 62 PATIENTS WITH BIPOLAR DEPRESSION AND 187 PATIENTS WITH UNIPOLAR MAJOR DEPRESSION IN REGARDS TO COMORBIDITIES AND OTHER MEASUREMENTS.

MEASUREMENTS	BIPOLAR DEPRESSION	UNIPOLAR MAJOR DEPRESSION	PEARSON'S EXACT TEST: 2-SIDED P-VALUE
Anxiety disorders	8 (16.1%)	72 (38.5%)	P<0.001
Current substance use disorders	5 (8.1%)	9 (4.8%)	P=0.346
Prior history of substance use disorders	18 (29.1%)	33 (17.6%)	P=0.0325
Personality disorders	9 (14.5%)	6 (3.2%)	P=0.0031
Risk factors for the metabolic syndrome	1 (1.6%)	21 (11.2%)	P=0.0094
Age group:18-35	30 (48.4%)	21 (11.2%)	P=0.0148
Age group: 36-49	21 (33.9%)	59 (31.6%)	P=0.7551
Age group: >50	11 (17.7%)	70 (37.4%)	P=0.0046
Gender (male: female)	23 (37.1%) :39 (62.9%)	59 (31.6%): 128 (68.4%)	P=0.4207
Unemployment	7 (11.3%)	29(15.5%)	P=0.8280
Marital status: single	16 (25.8%)	45 (24.0%)	P=0.8648
Reason for referral: depressed mood	29 (46.8%)	167 (89.3%)	P<0.001
Reason for referral: "mood swings of uncertain origin"	25 (40.3%)	2 (1.1%)	P<0.001
Prior history of UMDD	32 (51.6%)	116 (62.0%)	P<0.1792
Family history of mood disorders	18 (29.0%)	48 (25.7%)	P<0.6205

TABLE 2: COMPARING 62 PATIENTS WITH BIPOLAR DEPRESSION AND 39 PATIENTS WITH BIPOLAR SPECTRUM DISORDER IN REGARDS TO COMORBIDITIES AND OTHER MEASUREMENTS.

MEASUREMENTS	BIPOLAR DEPRESSION	BIPOLAR SPECTRUM DISORDER(DEPRESSED)	PEARSON'S EXACT TEST: 2-SIDED P-VALUE
Anxiety disorders	8 (16.1%)	5 (12.9%)	P=1.000
Current substance use disorders	5 (8.1%)	5 (12.9%)	P=N0.6638
Prior history of substance use disorders	18 (29.1%)	13 (33.4%)	P=0.7310
Personality disorders	9 (14.5%)	6 (15.4%)	P=1.000
Risk factors for the metabolic syndrome	1 (1.6%)	3 (7.6%)	P=0.2956
Age group: 18-49	51 (82.3%)	30 (77.0%)	P=0.6096
Gender (male: female)	23 (37.1%): 39 (62.9%)	13 (33.3%): 23 (66.7%)	P=0.8315
Unemployment	7 (11.3%)	12 (30.8%)	P=0.0176
Marital status: single	16 (25.8%)	15 (38.5%)	P=0.1919
Reason for referral: depressed mood	29 (46.7%)	16 (41.0%)	P=0.6817
Reason for referral: "mood swings of uncertain origin"	25 (40.3%)	17 (43.6%)	P=1.000
Prior history of UMDD	32(51.6%)	26 (66.7%)	P=0.1531
Family history of mood disorders	18 (29.0%)	8 (20.5%)	0.4836

13 REFERENCES AND BIBLIOGRAPHY

Agosti V, Stewart JW. Atypical and non-atypical subtypes of depression: comparison of social functioning, symptoms, course of illness, co-morbidity and demographic features.

J Affect Disord. 2001;(65):75-79.

Akiskal HS, Akiskal KK, Lancrenon S, Hantouche EG, Fraud JP, Gury C, Allilaire JF. Validating the bipolar spectrum in the French National EPIDEP Study: overview of the phenomenology and relative prevalence of its clinical prototypes.

J Affect Disord. 2006 Dec; 96(3):197-205.

Akiskal HS, Benazzi F. The DSM-IV and ICD-10 categories of recurrent (major) depressive and bipolar II disorders: evidence that they lie on a dimensional spectrum.

J Affect Disord. 2006 May;92(1):45-54.

Akiskal HS, Benazzi F. Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical wisdom.

J Clin Psychiatry. 2005 Jul;66(7):914-21.

Akiskal HS, Bourgeois ML, Angst J, Post R, Moller H, Hirschfeld R. Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders.
J Affect Disord. 2000 Sep;59 Suppl 1:S5-S30.

Akiskal HS, Pinto O. The evolving bipolar spectrum. Prototypes I, II, III, and IV. Psychiatr Clin North Am. 1999 Sep; 22(3):517-34.

Allilaire JF, Hantouche EG, Sechter D, Bourgeois ML, Azorin JM, Lancrenon S, Chatenet-Duchenne L, Akiskal HS. Frequency and clinical aspects of bipolar II disorder in a French multicenter study: EPIDEP.
Encephale. 2001 Mar-Apr;27(2):149-58.

Almeida OP, Fenner S. Bipolar disorder: similarities and differences between patients with illness onset before and after 65 years of age.
Int Psychogeriatr. 2002 Sep;14(3):311-22.

Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder.
J Clin Psychiatry. 2002;63:807-811.

American Psychiatric Association Practice Guidelines for the Treatment of Psychiatric disorders: Compendium 2002:555-613.

American Psychiatric Association Diagnostic And Statistical Manual of Mental disorders Fourth Edition 1994.

Angst J. The bipolar spectrum.
Br J. Psychiatry. 2007 Mar;190:189-91.

Angst J. Do many patients with depression suffer from bipolar disorder.
Can J Psychiatry. 2006:51:3-5.

Angst J, Gamma A, Lewinsohn P. The evolving epidemiology of bipolar disorder.
World Psychiatry. 2002 Oct;1(3):146-8.

Angst J, Marmeros A. bipolarity from ancient to modern times: conception, birth and rebirth.
J Affect disorder. 2001 Dec; 67(1-3):3-19.

Balazs J, Benazzi F, Rihmer A, Akiskal KK, Akiskal HS. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention.
J Affect Disord. 2006 Apr;91(2-3):133-8.

Baldassano C. Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder.
J Clin Psychiatry. 2006;67 (suppl11):8-11.

Baldassano C, Marangell L, Gyulai L et al. Gender differences in bipolar disorder; retrospective data from the first 500 STEP-BD participants.
Bipolar Disord. 2005;7:465-470.

Benazzi F. bipolar II disorder: epidemiology, diagnosis and management.
CNS Drugs. 2007;21(9):727-40.

Benazzi F. Borderline personality-bipolar spectrum relationship.
Prog Neuropsychopharmacol Biol Psychiatry. 2006 Jan;30(1):68-74.

Benazzi F. Testing atypical depression definitions.
Int J Methods Psychiatr Res. 2005; 14(2):82-91.

Benazzi F, Akiskal HS. A downscaled practical measure of mood lability as a screening tool for bipolar II.
J Affect Disord. 2005 Feb; 84(2-3):225-32.

Benazzi F. Female vs. male outpatient depression: a 448-case study in private practice.

Prog Neuropsychopharmacol Biol Psychiatry. 2000 Apr;24(3):475-81.

Benazzi F. The Montgomery-Asberg Depression Rating Scale in bipolar II and unipolar out-patients: a 405-patient case study.

Psychiatr Clin Neurosci.1999 Jun;53(3);429-31.

Berk M, Malhi GS, Cahill C, Carman AC, Hadzi-Pavlovic D, Hawkins MT, Tohen M, Mitchell PB. The bipolar depression rating scale (BDRS): it's development, validation and utility.

Bipolar Disord. 2007 Sep;9(6):571-9.

Berk M, Berk L, Moss K,Dodd S,Malhi GS. Diagnosing bipolar disorder: how can we do it better?

Med J Aust. 2006 May 1;184(9):459-62.

Berk M, Dodd S. bipolar II disorder: a review.

Bipolar Disord. 2005 Feb;7(1):11-21.

Berk M, Dodd S, Malhi GS.'bipolar missed states': the diagnosis and clinical salience of bipolar mixed states.

Aust N Z J Psychiatry. 2005 Apr;39(4):215-21.

Berk M, Ng F, Wang WV, Calabrese JR, Mitchell PB, Malhi GS, Tohen M. The empirical redefinition of the psychometric criteria for remission in bipolar disorder.

J Affect Disord.2007 Jul 25;[Epub ahead of print].

Carmody TJ, Rush AJ, Bernstein IH, Brannan S, Burnham D, Woo A, Trivedi MH. The Montgomery Asberg and the Hamilton ratings of depression; a comparison of measures.

Eur Neuropsychopharmacol. 2006 Dec;16(8):601-11.

Carmody TJ, Rush AJ,Bernstein IH, Brannan S, Husain MM, Trivedi MH. Making clinicians lives easier: guidance on use of the QIDS self-report in place of the MADRS.

J Affect Disord. 2006 Oet;95:115-8.

Chang KD, Steiner H, Ketter TA: Psychiatric phenomenology of child and adolescent bipolar offspring.

J Acad Child Adolesc Psychiatry. 2000; 39;453-460.

Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character.

Arch. Gen Psychiatry. 1993; (50):975-990.

Davidson JRT. A history of the concept of atypical depression.
J Clin Psychiatry. 2007;68(suppl 3):10-15.

De Leon J, Diaz FJ. Planning for the optimal design of studies to personalize antipsychotic prescriptions in the post-CATIE era: The clinical and pharmacoepidemilogical data suggest that pursuing the pharmacogenetics of metabolic syndrome complications (hypertension, diabetes mellitus and hyperlipidemia) may be a reasonable strategy.
Schizophr Res. 2007 Nov;96(1-3):185-197.

Derry S, Moore RA. Atypical antipsychotics in bipolar disorder: systematic review of randomized trials.
BMC Psychiatry. 2007 Aug 16;7:40.

Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E. Obesity as a correlate of outcome in patients with bipolar I disorder.
Am J Psychiatry. 2003 Jan;160(1):112-7.

Ghaemi SN, Baldessarini RJ. The manic-depressive spectrum and mood stabilization: Kraepelin's ghost.
Psychother Psychosom. 2007;76(2):65-9.

Ghaemi SN, Miller CJ, Rosenquist KJ, Pies R. Sensitivity and specificity of the Bipolar Spectrum Diagnostic Scale for detecting bipolar disorder.
J Affect. Disord. 2005; 84:273-77.

Ghaemi SN, Hsu DJ, Ko JY, Baldassano CF. Kontos NJ, Goodwin FK. Bipolar spectrum disorder: a pilot study.
Psychopathology. 2004 Sep-Oct;37(5):222-6.

Ghaemi SN, Ko JY, Goodwin FK. "Cade's Disease" and beyond: Misdiagnosis, Antidepressant Use, and a Proposed Definition for bipolar spectrum disorder.
Can J Psychiatry. 2002; 47: 125-134.

Ghaemi SN, Ko Jy, Goodwin FK. The bipolar spectrum and the antidepressant view of the world.
J Psychiatr Pract. 2001 Sep;7(5):287-97.

Grant BF, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiological Survey on Alcohol and Related Conditions.
J Clin Psychiatry. 2005 Oct;66(10):1205-15.

Gunderson JG, Weinberg I, Daversa MT, Kueppenbender KD, Zanarini MC, Shea MT, Skodol AE, Sanislow CA, Yen S, Morey LC, Grilo CM, McGlashan TH, Stout RL, Dyck I. Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder.
Am J Psychiatry. 2006 Jul;163(7):1173-8. Erratum in: Am J Psychiatry.2006 Oct;163(10):1843.

Hamilton M. A rating scale for depression.
J Neurol Neurosurg Psychiatry. 1960 Feb;23:56-62.

Hendrick V, Altshuler LL, Gitlin MJ, Delrahim S, Hammen C. Gender and bipolar illness.
J Clin Psychiatry. 2000 May; 61(5): 393-6.

Henry C, Van den Bulke D, Bellivier F, et al. Anxiety disorder comorbidity in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer.
J Clin Psychiatry. 2003;64:331-335.

Hirschfeld RM. Calabrese JR, Weissman MM, Reed M, Davies MA, Frye MA, Keck PE Jr, Lewis L, McElroy SL, McNulty JP, Wagner KD. Screening for bipolar disorder in the community.
J Clin Psychiatry. 2003 Jan;64(1):53-9.

Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE jr, Lewis L, McElroy SL, Post RM, Rapport DJ, Russell JM, Sachs GS, Zajecka J. Development and validation of a screening instrument for bipolar disorder: the mood disorder questionnaire.
Am J Psychiatry. 2000 Nov;157(11):1873-5.

Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF. Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study.
Psychiatr Res. 2006 Dec 7;145(2-3):155-67.

Holtzheimer PE, Mayberg HS. Neuropsychiatric aspects of mood disorders.
The American psychiatric publishing textbook of neuropsychiatry and behavioral neurosciences Fifth edition 2008, Chapter 27:1003-24.

Judd LL, Akiskal HS, Schettler PJ, Endicott J, Leon AC, Solomon DA, Coryell W, Maser JD, Keller MB. Psychosocial disability in the course of bipolar I and II disorders: a prospective, comparative, longitudinal study.
Arch Gen Psychiatry. 2005 Dec;62(12):1322-30.

Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder.
Arch Gen Psychiatry. 2003;60:261-269.

Judd LL, Akiskal HS, Schettler PJ, et al. The Long-term Natural History of the Weekly Symptomatic Status of bipolar 1 disorder.
Arch Gen Psychiatr. 2002; 59:530-537.

Kaplan and Sadock's synopsis of psychiatry, eighth edition 1998, Chapter 15, page 538-9.

Keller MB. Prevalence and impact of comorbid anxiety and bipolar disorder.
J Clin Psychiatry. 2006;67 suppl 1:5-7.

Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG. Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey.
Br J Psychiatry. Suppl 1996;30:17-30.

Kessing LV. Diagnostic subtypes of older versus younger adults.
Bipolar Disord. 2006 Feb;8(1):56-64.

Kiejna A, Rymaszewska J, Hadrys T, Suwalska A, Lojko D, Rybakowski JK. [bipolarity among unipolar affective disorder patients—uniDEP-BI national multi-site study].
Psychiatr Pol. 2005 Sep-Oct; 39(5):951-62.

Kleinman L, Lowin A, Flood E, Gandhi G, Edgell E, Revicki D. Costs of bipolar disorder.

Pharmacoeconomics. 2003;21(9): 601-22.

Lara DR, Pinto O, Akiskal K, Akiskal HS. Toward an integrative model of the spectrum of mood, behavioral and personality disorders based on fear and anger traits: I. Clinical implications.

J Affect Disord. 2006 Aug;94(1-3):67-87.

Liebowitz MR, Klein DF. Hysteroid dysphoria.

Psychiatr Clin North Am. 1979;(2):555-575.

Maina G, Albert U, Bellodi L, Colombo C, Faravelli C, Monteleone P, Bogetto F, Cassano G, Maj M. Health-related quality of life in euthymic bipolar disorder patients: differences between bipolar I and II subtypes.

J Clin Psychiatry. 2007 Feb;68(2):207-12.

Magill CA. The boundary between borderline personality disorder and bipolar disorder: current concepts and challenges.

Can J Psychiatry. 2004 Aug;49(8):551-6.

Mantere O, Melartin TK, Suominen K, Rytsala HJ, Valtonen HM, Arvilommi P, Leppamaki S, Isometsa ET. Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder.
J Clin Psychiatry. 2006 Apr; 67(4):584-93.

McElroy SL, Kotwal R, Keck PE Jr, Akiskal HS. Comorbidity of bipolar and eating disorders: distinct or related disorders with shared dysregulations?
J Affect Disord. 2005 Jun;86(2-3):107-27.

McElroy SL. Diagnosing and treating comorbid (complicated) bipolar disorder.
J Clin Psychiatry. 2004 65(suppl 15):35-44.

McElroy SL, Altshuler LL, Suppes T, et al. Axis 1 psychiatric comorbidity and its relationship to historical variables in 288 patients with bipolar disorder.
Am J Psychiatry. 2001;158:420-426.

McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Interaction Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III.
Schizophr Res. 2005;80:19-32.

McIntyre RS, Soczynska JK, Beyer JL, Woldeyohannes HO, Law CW, Miranda A, Konarski JZ, Kennedy SH. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs.
Curr Opin Psychiatry. 2007 Jul; 20(4):406-16.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirshfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication.
Arch Gen Psychiatry. 2007 May; 64(5):543-52.

Mitchell JD, Brown ES, Rush AJ. Comorbid disorders in patients with bipolar disorder and concomitant substance dependence.
J Affect Disord. 2007 Sep; 102(1-3):281-7.

Moller HJ, Schnitker J. [Prospective study using a modified Montgomery-Asberg Depression Scale].
Nervenarzt. 2007 Jun;78(6):685-90.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change.
Br J Psychiatry. 1979;134:382-389.

Muller MJ, Szegedi A, Wetzel H, Benkert O. Moderate and severe depression. Gradations for the Montgomery-Asberg Depression Rating Scale.
J Affect Disord. 2000 Nov;60(2):137-40.

Muzina DJ. Bipolar spectrum disorder: differential diagnosis and treatment.
Prim Care Clin Office Pract. 2007 (34):521-50.

Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence.
J Clin Psychiatry.2007;68 Suppl 1:20-7.

Newcomer J. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review.
CNS Drugs. 2005;19 (suppl 1):1-93.

Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants.
Biol Psychiatry. 2005;57:1467-1473.

Othmer E, Desouza CM, Penick EC, Nickel EJ, Hunter EE, Othmer SC,Powell BJ, Hall SB. Indicators of mania in depressed outpatients: a retrospective analysis of data from the KANSAS 1500 study.
J Clin Psychiatry. 2007 Jan;68(1);47-51.

Paris J, Gunderson J, Weinberg I. The interface between borderline personality disorder and bipolar spectrum disorders.
Compr Psychiatry. 2007 Mar-Apr;48(2):143-54.

Parker GB. Atypical Depression: a Valid Subtype?
J Clin Psychiatry 2007; 68 (suppl 3):18-22.

Patten SB. Does almost everybody suffer from a bipolar disorder?
Can J Psychiatry. 2006:51:6-8.

Peele PB, Xu Y, Kupfer DJ. Insurance expenditures on bipolar disorder: clinical and parity implications.
Am J Psychiatry. 2003 Jul;160(7):1286-90.

Perugi G, Akiskal HS, Latanzi L, et al. The high prevalence of of "soft" bipolar (II) features in atypical depression.
Compr Psychiatry. 1998;39:63-71.

Pickering RP, Grant BF, Chou SP, Compton WM. Are overweight, obesity, and extreme obesity associated with psychopathology? Results from the national epidemiologic survey on alcohol and related conditions.
J Clin Psychiatry. 2007 Jul;68(7):998-1009.

Post RM. The impact of bipolar depression.
J Clin Psychiatry. 2005; 66 (suppl 5):5-10.

Rybakowski JW, Suwalska A, Lojko D, Rymaszewska J, Kiejna A.
Types of depression more frequent in bipolar than in unipolar affective illness: results of the Polish DEP-BI study.
Psychopathology. 2007;40(3):153-8.

Sachs GS, Baldassano CF, Truman BA, Guille C. Comorbidity of attention-deficit hyperactivity disorder with early-and late-onset bipolar disorder.
Am J Psychiatry. 2000 Mar;157(3):466-8.

Schaffer A, Cairney J, Cheung A, Veldhuizen S, Levitt A. Comminity Survey of bipolar disorder in Canada: Lifetime prevalence and illness characteristics.
Can J Psychiatry. 2006:51:9-16.

Schurhoff F, Bellivier F, Jouvent R, Mouren-Simeoni MC, Bouvard M, Allilaire JF, Leboyer M. Early and late onset bipolar disorders: two different forms of manic-depressive illness?
J Affect Disord. 2000; 58(3): 215-21.

Silverstone PH, Entsuah R, Hackett D. Two items on the Hamilton Depression rating scale are effective predictors of remission: comparison of selective serotonin reuptake inhibitors with the combined serotonin/norepineprine reuptake inhibitor, venlafaxine.
Int Clin Psychopharmacol. 2002 Nov; 17(6):273-80.

Simon GE, Bauer MS, Ludman EJ, Operskalski BH. Unutzer J. Mood symptoms, functional impairment and disability in people with bipolar disorder: specific effects of mania and depression.
J Clin Psychiatry. 2007, Aug;68(8):1237-45.

Simon NM, Zalta AK, Otto MW, OstacherMJ, Fischmann D, Chow CW, Thompson EH, Stevens JC, Demopulos CM, Nierenberg AA, Pollack MH. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder.
J Psychiatr Res. 2007 Apr-Jun;41(3-4):255-64.

Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).
Am J Psychiatry 2004. 161:2222-9.

Stone MH. Relationship of borderline personality disorder and bipolar disorder.
Am J Psychiatry. 2006 Jul;16397):1126-8.

Suppes T, Kelly DI, Perla JM. Challenges in the management of bipolar depression.
J Clin Psychiatry. 2005;66 (suppl 5): 11-16.

Tabuse H, Kalali A, Azuma H, Ozaki N, Iwata N, Naitoh H, Higuchi T, Kamba S, Shioe K, Akechi T, Furukawa TA. The new GRID Hamilton Rating Scale for Depression demonstrates excellent inter-reliability for inexperienced and experienced raters before and after training.
Psychiatry Res. 2007 Sep 30;153(1):61-7.

Taylor V, MacQueen G. Associations between bipolar disorder and metabolic syndrome: a review.
J Clin Psychiatry. 2006 Jul;67(&):1034-41.

Thase ME. New directions in the treatment of atypical depression.
J Clin Psychiatry. 2007;68 (suppl3): 4-7.

Thase ME. Recognition and diagnosis of atypical depression.
J Clin Psychiatry. 2007;68 (suppl 8): 11-16.

Tillman R, Geller B. Controlled study of switching from attention-deficit/hyperactivity disorder to a prepubertal and early adolescent bipolar I disorder phenotype during 6-year follow-up: rate, risk, and predictors.
Dev Psychopathol. 2006 Fall; 18(4):1037-53.

Utsumi T, Sasaki T, Shimada I, Mabuchi M, Motonoga T, Ohtani T, Tochigi M, Kato N, Nanko S. Clinical features of soft bipolarity in major depressive inpatients.
Psychiatry Clin Neurosci. 2006 Oct;60(5):611-5.

Valtonen H, Suominen K, Mantere O, Leppamaki S. Arvilommi P, Isometsa ET. Suicidal ideation and attempts in bipolar I and II disorders.
J Clin Psychiatry. 2005 Nov;66(11):1456-62.

Vieta E, Colom F, Corbella B, et al. Clinical correlates of psychiatric comorbidity in bipolar I patients.
Bipolar Disord. 2001;3:253-528.

Vieta E, Colom F, Martinez-Aran A, et al. Bipolar II disorder and comorbidity. Compr Psychiatry. 2000;41:339-343.

Yatham LN, Kennedy SH, O'Donovan C, Parikh SV, MacQueen G, McIntyre RS, Sharma V, Beaulieu S; Guidelines group, CANMAT. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: update 2007.
Bipolar Disord. 2006 Dec;8(6):721-39.

Yatham LN, Kennedy SH, O'Donovan C, Parikh S, MacQueen G, McIntyre R, Sharma V, Silverstone P, Alda M, Baruch P, Beaulieu S, Daigneault A, Miley R, Young LT, Ravindren A, Schaffer A, Connolly M, Gormon CP. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord. 2005;7 suppl3:5-69.

Zimmerman M, Posternak MA, Chelminski I. Derivation of a definition of remission on the Montgomery-Asberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression.
J Psychiatr Res. 2004 Nov-Dec;38(6):577-82.